

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 January 2007 (04.01.2007)

PCT

(10) International Publication Number  
**WO 2007/002543 A2**

(51) International Patent Classification: **Not classified**

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(21) International Application Number:  
PCT/US2006/024717

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 23 June 2006 (23.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/693,603 23 June 2005 (23.06.2005) US  
60/699,614 15 July 2005 (15.07.2005) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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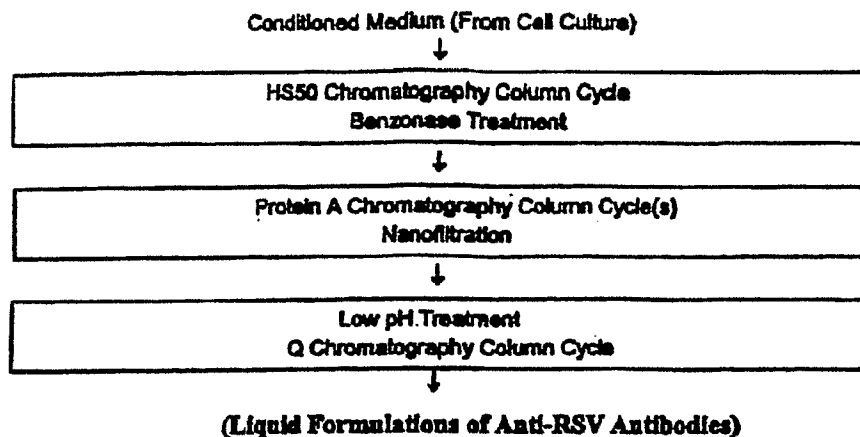
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**Published:**

— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: ANTIBODY FORMULATIONS HAVING OPTIMIZED AGGREGATION AND FRAGMENTATION PROFILES



(57) Abstract: The present invention provides methods of optimizing the production and purification of antibody formulations that immunospecifically bind to antigens of interest and are suitable for parenteral administration to a subject, which formulations exhibit increased stability due to reduced degradation and aggregation of the antibody component on long term storage. Such methods provide formulations that offer multiple advantages over formulations produced by non-optimized methods including less stringent or more readily available transportation/storage conditions, and less frequent dosing or smaller dosage amounts in the therapeutic, prophylactic and diagnostic use of such formulations. The invention further provides methods of utilizing the formulations of the present invention.

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**ANTIBODY FORMULATIONS HAVING OPTIMIZED  
AGGREGATION AND FRAGMENTATION PROFILES**

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This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/693,603, filed on June 23, 2005, and U.S. Provisional Patent Application No. 60/699,614, filed on July 15, 2005, each of which is incorporated by reference herein in its entirety.

1. **INTRODUCTION**

[0001] The present invention provides methods of optimizing the production and purification of antibody formulations that immunospecifically bind to antigens of interest and are suitable for parenteral administration to a subject, which formulations exhibit increased stability due to reduced degradation and aggregation of the antibody component on long term storage. Such methods provide formulations that offer multiple advantages over formulations produced by non-optimized methods including less stringent or more readily available transportation/storage conditions, and less frequent dosing or smaller dosage amounts in the therapeutic, prophylactic and diagnostic use of such formulations. The invention further provides methods of utilizing the formulations of the present invention. In a specific embodiment, the invention provides methods of optimizing the production and purification of antibody formulations that immunospecifically bind to RSV antigens, which formulations exhibit increased stability due to reduced degradation and aggregation of the antibody component on long term storage. Such formulations may be used in the diagnostic, therapeutic or prophylactic treatment of RSV infections.

2. **BACKGROUND OF THE INVENTION**

**Respiratory Syncytial Virus**

[0002] Respiratory infections are common infections of the upper respiratory tract (*e.g.*, nose, ears, sinuses, and throat) and lower respiratory tract (*e.g.*, trachea, bronchial tubes, and lungs). Symptoms of upper respiratory infection include runny or stuffy nose, irritability, restlessness, poor appetite, decreased activity level, coughing, and fever. Viral upper respiratory infections cause and/or are associated with sore throats, colds, croup, and the flu. Clinical manifestations of a lower respiratory infection include shallow coughing that produces sputum in the lungs, fever, and difficulty breathing.

[0003] Respiratory syncytial virus (RSV) is one of the leading causes of respiratory disease worldwide. In the United States, it is responsible for tens of thousands of hospitalizations and thousands of deaths per year (see Black, C.P., *Resp. Care* 2003 48(3):209-31 for a recent review of the biology and management of RSV). Infants and children are most at risk for serious RSV infections which migrate to the lower respiratory system, resulting in pneumonia or bronchiolitis. In fact, 80% of childhood bronchiolitis cases and 50% of infant pneumonias are attributable to RSV. The virus is so ubiquitous and highly contagious that almost all children have been infected by two years of age. Although infection does not produce lasting immunity, reinfections tend to be less severe so that in older children and healthy adults RSV manifests itself as a cold or flu-like illness affecting the upper and/or lower respiratory system, without progressing to serious lower respiratory tract involvement. However, RSV infections can become serious in elderly or immunocompromised adults. (Evans, A.S., eds., 1989, *Viral Infections of Humans. Epidemiology and Control*, 3<sup>rd</sup> ed., Plenum Medical Book, New York at pages 525-544; Falsey, A.R., 1991, *Infect. Control Hosp. Epidemiol.* 12:602-608; and Garvie et al., 1980, *Br. Med. J.* 281:1253-1254; Hertz et al., 1989, *Medicine* 68:269-281).

[0004] At present, there is no vaccine against RSV, nor is there any effective treatment. Recent clinical data has failed to support the early promise of the antiviral agent ribavirin, which is the only drug approved for treatment of RSV infection (Black, C.P., *Resp. Care* 2003 48(3):209-31). Consequently, the American Academy of Pediatrics issued new guidelines suggesting that use of ribavirin be restricted to only the most severe cases (Committee on Infectious Disease, American Academy of Pediatrics. 1996. *Pediatrics* 97:137-140; Randolph, A.G., and E.E. Wang., 1996, *Arch. Pediatr. Adolesc. Med.* 150:942-947).

[0005] While a vaccine or effective treatment have proven elusive, some success has been achieved in the area of prevention for infants at high risk of serious upper and/or lower respiratory tract RSV infection. In particular, there are two immunoglobulin-based therapies approved to protect high-risk infants from serious lower respiratory tract RSV infection, RSV-IGIV (RSV-immunoglobulin intravenous, also known as RespiGam™) and palivizumab (SYNAGIS®). However, neither RSV-IGIV nor palivizumab has been approved for use other than as a prophylactic agent for lower respiratory tract RSV infections.

[0006] RSV is easily spread by physical contact with contaminated secretions. The virus can survive for at least half an hour on hands and for hours on countertops and used tissues. The highly contagious nature of RSV is evident from the risk factors associated with contracting serious infections. One of the greatest risk factors is hospitalization, where in some cases in

excess of 50% of the staff on pediatric wards were found to be infected (Black, C.P., *Resp. Care* 2003 48(3):209-31). Up to 20% of these adult infections are asymptomatic but still produce substantial shedding of the virus. Other risk factors include attendance at day care centers, crowded living conditions, and the presence of school-age siblings in the home. Importantly, an agent that is effective at clearing the virus from the upper and/or lower respiratory tract is likely to be effective in preventing its transmission. Thus, one promising approach to preventing serious RSV infections is the development of therapies to clear or block the virus from the upper and/or lower respiratory tract.

**[0007]** Although RSV-IVIG and palivizumab represent significant advances in the prevention of lower respiratory tract RSV infections, neither has demonstrated efficacy at permissible doses against the virus in the upper respiratory tract. In fact, RSV-IVIG failed to clear nasal RSV when administered as a nasal spray in amounts that were effective to clear pulmonary RSV in every animal of the treatment group (Prince et al., U.S. Patent No. 4,800,078, issued January 24, 1989). The interperitoneal route of administration also failed to clear RSV from the upper respiratory tract with the same efficacy as the lower respiratory tract. It has recently been noted that the immune response elicited by upper respiratory tract infections differs from that induced by lower respiratory infections (van Benten I.J. et al., *J. Med. Virol.* 2003 Oct.;71(2):290-7). Thus, a need exists for the prevention and treatment of upper and/or lower respiratory tract RSV infections.

### **Otitis Media**

**[0008]** Otitis media is an infection or inflammation of the middle ear. This inflammation often begins when infections that cause sore throats, colds, or other respiratory or breathing problems spread to the middle ear. These can be viral or bacterial infections. RSV is the principal virus that has been correlated with otitis media. Seventy-five percent of children experience at least one episode of otitis media by their third birthday. Almost half of these children will have three or more ear infections during their first 3 years. It is estimated that medical costs and lost wages because of otitis media amount to \$5 billion a year in the United States (Gates GA, 1996, Cost-effectiveness considerations in otitis media treatment. *Otolaryngol Head Neck Sur.* 114 (4): 525-530). Although otitis media is primarily a disease of infants and young children, it can also affect adults.

**[0009]** Otitis media not only causes severe pain but may result in serious complications if it is not treated. An untreated infection can travel from the middle ear to the nearby parts of the head, including the brain. Although the hearing loss caused by otitis media is usually



temporary, untreated otitis media may lead to permanent hearing impairment. Persistent fluid in the middle ear and chronic otitis media can reduce a child's hearing at a time that is critical for speech and language development. Children who have early hearing impairment from frequent ear infections are likely to have speech and language disabilities.

[0010] Although many physicians recommend the use of antibiotics for the treatment of ear infections, antibiotic resistance has become an important problem in effective treatment of the disease. Further, new therapies are needed to prevent or treat viral infections that are associated with otitis media, particularly RSV.

### **Asthma and Reactive Airway Disease (RAD)**

[0011] About 12 million people in the U.S. have asthma and it is the leading cause of hospitalization for children. *The Merck Manual of Diagnosis and Therapy* (17th ed., 1999).

[0012] Asthma is an inflammatory disease of the lung that is characterized by airway hyperresponsiveness ("AHR"), bronchoconstriction (*i.e.*, wheezing), eosinophilic inflammation, mucus hypersecretion, subepithelial fibrosis, and elevated IgE levels. Asthmatic attacks can be triggered by environmental triggers (*e.g.* acarids, insects, animals (*e.g.*, cats, dogs, rabbits, mice, rats, hamsters, guinea pigs, mice, rats, and birds), fungi, air pollutants (*e.g.*, tobacco smoke), irritant gases, fumes, vapors, aerosols, chemicals, or pollen), exercise, or cold air. The cause(s) of asthma is unknown. However, it has been speculated that family history of asthma (London *et al.*, 2001, *Epidemiology* 12(5):577-83), early exposure to allergens, such as dust mites, tobacco smoke, and cockroaches (Melen *et al.*, 2001, 56(7):646-52), and respiratory infections (Wenzel *et al.*, 2002, *Am J Med*, 112(8):672-33 and Lin *et al.*, 2001, *J Microbiol Immunol Infect*, 34(4):259-64), such as RSV, may increase the risk of developing asthma. A review of asthma, including risk factors, animal models, and inflammatory markers can be found in O'Byrne and Postma (1999), *Am. J. Crit. Care. Med.* 159:S41-S66, which is incorporated herein by reference in its entirety.

[0013] Current therapies are mainly aimed at managing asthma and include the administration of  $\beta$ -adrenergic drugs (*e.g.* epinephrine and isoproterenol), theophylline, anticholinergic drugs (*e.g.*, atropine and ipratropium bromide), corticosteroids, and leukotriene inhibitors. These therapies are associated with side effects such as drug interactions, dry mouth, blurred vision, growth suppression in children, and osteoporosis in menopausal women. Cromolyn and nedocromil are administered prophylactically to inhibit mediator release from inflammatory cells, reduce airway hyperresponsiveness, and block responses to allergens.

However, there are no current therapies available that prevent the development of asthma in subjects at increased risk of developing asthma. Thus, new therapies with fewer side effects and better prophylactic and/or therapeutic efficacy are needed for asthma.

[0014] Reactive airway disease is a broader (and often times synonymous) characterization for asthma-like symptoms, and is generally characterized by chronic cough, sputum production, wheezing or dyspnea.

### **Wheezing**

[0015] Wheezing (also known as sibilant rhonchi) is generally characterized by a noise made by air flowing through narrowed breathing tubes, especially the smaller, tight airways located deep within the lung. It is a common symptom of RSV infection, and secondary RSV conditions such as asthma and bronchiolitis. The clinical importance of wheezing is that it is an indicator of airway narrowing, and it may indicate difficulty breathing.

[0016] Wheezing is most obvious when exhaling (breathing out), but may be present during either inspiration (breathing in) or exhalation. Wheezing most often comes from the small bronchial tubes (breathing tubes deep in the chest), but it may originate if larger airways are obstructed.

[0017] Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

### **3. SUMMARY OF THE INVENTION**

[0018] The present invention is based upon the inventors' use of sensitive analytical techniques, such as analytical ultracentrifugation (AUC), size exclusion chromatography (SEC), Liquid Chromatography Mass Spectrometry (LC-MS) or particle counter analysis to analyze the fragmentation and aggregation profiles of formulations of full-length IgG1 monoclonal antibodies, particularly those that have been recombinantly expressed in myeloma cells, such as, but not limited to, NS0 cells. Thus, the present invention provides antibody formulations having fragmentation and aggregation profiles that are improved (*i.e.*, have decreased total fragmentation and/or aggregation or have decreased amounts of certain types of fragments or aggregates or have reduced rates of aggregation or fragmentation) as compared to prior antibody formulations.

[0019] In a particular embodiment, the invention provides an antibody formulation comprising a full length IgG<sub>1</sub> antibody, preferably specific for a therapeutic or prophylactic target, wherein no more than 0.5 % of the total protein fraction (in certain embodiments, however, at least 0.1% of the total protein fraction or is below detectable levels) of said formulation comprises (or, in other embodiments, consists of as impurities or as fragments to detectable levels) antibody type I fragments. In other embodiments, no more than 0.5% of the total protein fraction (and, in certain embodiments, at least 0.1% of the total protein fraction or is below detectable levels) of said formulation comprises (or, in other embodiments, consists of as impurities or as fragments to detectable levels) antibody type I fragments and antibody type II fragments. Preferably, the antibody type I fragments comprise one or more C-terminal portions of the heavy chain of the antibody, which heavy chain C-terminal portion has a molecular weight of about 25.6 kD, about 25.7 kD, about 25.8 kD, about 26.0 kD, or about 26.1 kD as determined by Liquid Chromatography Mass Spectrometry (LC-MS) analysis of samples of the antibody that have been deglycosylated, reduced and alkylated. Moreover, the antibody type II fragments comprise one or more N-terminal portions of the heavy chain of the antibody, which heavy chain N-terminal portion has a molecular weight of about 24.4 kD, about 24.6 kD, about 24.7 kD, about 24.9 kD, or about 25.1 kD as determined by LC-MS analysis of samples of the antibody that have been deglycosylated, reduced and alkylated. In addition, the antibody type I fragments may comprise one or more C-terminal portions of the heavy chain, which heavy chain C-terminal portion comprises amino acid residues 223-449 of the IgG<sub>1</sub> heavy chain (according to Kabat numbering), amino acid residues 224-449 of the IgG<sub>1</sub> heavy chain, amino acid residues 225-449 of the IgG<sub>1</sub> heavy chain, amino acid residues 226-449 of the IgG<sub>1</sub> heavy chain, amino acid residues 227-449 of the IgG<sub>1</sub> heavy chain, amino acid residues 228-449 of the IgG<sub>1</sub> heavy chain and amino acid residues 229-449 of the IgG<sub>1</sub> heavy chain and the antibody type II fragments comprise one or more heavy chain N-terminal portions which comprises amino acid residues 1-222 of the IgG<sub>1</sub> heavy chain, amino acid residues 1-223 of the IgG<sub>1</sub> heavy chain, amino acid residues 1-224 of the IgG<sub>1</sub> heavy chain, amino acid residues 1-225 of the IgG<sub>1</sub> heavy chain, amino acid residues 1-226 of the IgG<sub>1</sub> heavy chain, amino acid residues 1-227 of the IgG<sub>1</sub> heavy chain or amino acid residues 1-228 of the IgG<sub>1</sub> heavy chain. In certain embodiments, the antibody formulation does not contain detectable levels of any other types of fragments. In certain embodiments, the antibody formulation contains one, two, three, four, five, six or seven of the type I fragments and/or contains one, two, three, four, five, six or seven of the type II fragments.

**[0020]** In particular embodiments, the formulations of the invention comprise (or consists of as the aggregate fraction) a particle profile of less than about  $3.4 \times 10^5$  particles/ml of diameter 2-4  $\mu\text{m}$ , less than about  $4.0 \times 10^4$  particles/ml of diameter 4-10  $\mu\text{m}$ , less than about  $4.2 \times 10^3$  particles/ml of diameter 10-20  $\mu\text{m}$ , less than about  $5.0 \times 10^2$  particles/ml of diameter 20-30  $\mu\text{m}$ , less than about  $7.5 \times 10^1$  particles/ml of diameter 30-40  $\mu\text{m}$ , and less than about  $9.4 \times 10^0$  particles/ml of diameter 40-60  $\mu\text{m}$  as determined by a particle multisizer. In certain embodiments, the formulation contains no detectable particles greater than 40  $\mu\text{m}$ , or greater than 30  $\mu\text{m}$ . In other embodiments, the formulations of the invention have a turbidity value of a degassed sample of said formulation of about 6.4 NTU (in certain embodiments from 4-8 NTU, in other embodiments less than 10 NTU, less than 8 NTU, less than 7 NTU, or less than 6.5 NTU).

**[0021]** The antibody formulations of the invention may likewise have a combination of one or more of the above parameters of fragmentation and aggregation.

**[0022]** The antibody formulations of the invention are preferably at least 10 mg/ml antibody, more preferably, 15 mg/ml, 25 mg/ml, 50 mg/ml, 75 mg/ml, 100 mg/ml, 150 mg/ml or 200 mg/ml. The antibody in the antibody formulations of the invention may be any antibody that has a therapeutic, prophylactic or diagnostic utility. In preferred embodiments, the antibody in the formulations of the invention is specific for RSV and, in a specific embodiment, is not palivizumab. In more specific and preferred embodiments, the anti-RSV antigen binds to the F protein of RSV, and, in particular embodiments, the RSV antigen comprises or even consists of the F protein epitope NSELLSLINDMPITNDQKKLMSNN (SEQ ID NO:337). In other embodiments, the antibody is one of the antibodies listed in Table 2, preferably is the antibody A4B4L1FR-S28R or competes for binding with one of the antibodies listed in Table 2, preferably A4B4L1FR-S28R.

**[0023]** The antibody formulations of the invention preferably maintain improved aggregation and fragmentation profiles upon storage, for example, for extended periods (for example, but not limited to 6 months, 1 year, 2 years, 3 years or 5 years) at room temperature or 4°C or for periods (such as, but not limited to 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months or 1 year) at elevated temperatures such as 38°C-42°C. Such formulations may be at pH 5-7, preferably at pH 6.0. Thus, in a particular embodiment, an antibody formulation of the invention comprising a full length IgG<sub>1</sub> antibody, upon storage at 38-42°C, pH 6.0 for 1 month, 6 months, 9 months or 14 months, comprises or, alternatively consists (other than the full length IgG<sub>1</sub> antibody or as the fragment fraction) one or more antibody type I

fragments. In another particular embodiment, an antibody formulation of the invention comprising a full length IgG<sub>1</sub> antibody, upon storage at 38-42°C, pH 6.0 for 1 month, 6 months, 9 months or 14 months, comprises or, alternatively consists (other than the full length IgG<sub>1</sub> antibody or as the fragment fraction) one or more antibody type I fragments and one or more antibody type II fragments. Upon storage, the level of fragments as a percentage of the total amount of protein is preferably less than 0.5% and, in certain embodiments is at least 0.1% or is below detectable levels of fragments.

**[0024]** Additionally, during storage, such formulations preferably exhibit constant aggregation and fragmentation rates at temperatures, such as, but not limited to, 0-4°C, 10-15°C, 20-24°C room temperature, or elevated temperatures 38-42°C, and extended periods, such as, but not limited to, two weeks, one month, six months, one year, three years or five years. In certain embodiments, the antibody formulation does not contain detectable levels of any other types of fragments. Thus, in a particular embodiment, an antibody formulation of the invention comprising a full length IgG<sub>1</sub> will increase in aggregate percentage relative to total protein, by 0.2%/month - 0.35%/month at 20-24°C and preferably by not more than 0.02%/month at 4 °C. In a further embodiment, an antibody formulation of the invention comprising a full length IgG<sub>1</sub> will not increase in fragment percentage, relative to total protein, by more than 0.015%/month - 0.03%/month at 20-24 °C and preferably by not more than 0.00%/month at 4 °C. In certain embodiments, the antibody formulation contains one, two, three, four, five or six or the type I fragments and/or contains one, two, three, four, five, six or seven of the type II fragments.

**[0025]** In particular embodiments, after storage, the formulations of the invention comprise (or consists of as the aggregate fraction) a particle profile of less than about 3.4 E +5 particles/ml of diameter 2-4 µm, less than about 4.0 E +4 particles/ml of diameter 4-10 µm, less than about 4.2 E +3 particles/ml of diameter 10-20 µm, less than about 5.0 E +2 particles/ml of diameter 20-30 µm, less than about 7.5 E +1 particles/ml of diameter 30-40 µm, and less than about 9.4 particles/ml of diameter 40-60 µm as determined by a particle multisizer. In certain embodiments, the formulation contains no detectable particles greater than 40 µm, or greater than 30 µm. In other embodiments, the formulations of the invention, after storage, have a turbidity value of a degassed sample of said formulation of about 6.4 NTU (in certain embodiments from 4-8 NTU, in other embodiments less than 10 NTU, less than 8 NTU, less than 7 NTU, or less than 6.5 NTU).

**[0026]** The antibody formulations of the invention, after storage, may likewise have a combination of one or more of the above parameters of fragmentation and aggregation.

**[0027]** Other aspects of the invention provide for methods of optimizing a particular antibody formulation for the fragmentation and aggregation parameters set forth above. Such methods comprise production, purification and formulation of the antibody and monitoring at one or more steps, or of the final formulation, for the levels of fragmentation and/or aggregation using methods such as, but not limited to AUC, SEC, LC-MS or particle multisizing, and then varying one or more parameters of one or more steps of the production, purification and/or formulation process or the formulation itself and evaluating whether varying the parameter reduces the level of fragmentation and/or aggregation. By such screening and monitoring steps, the method of the invention may be used to optimize an antibody formulation. Such parameters include, the temperature at which one or more steps is carried out, the reduction in or elimination of freeze/thaw cycles of the antibody, introduction of filtration steps, such as ultrafiltration, addition or change in one or more column chromatography steps, change in pH, etc.

**[0028]** The invention provides an antibody comprising a Fab fragment, which immunospecifically binds to an RSV antigen (e.g., the F protein epitope NSELLSLINDMPITNDQKKLMSNN (SEQ ID NO:337)), wherein the  $T_m$  of the Fab fragment is at least about 87 °C, and wherein said antibody is not any of palivizumab, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and A17h4. In a specific embodiment, the Fab in such an antibody is different from the Fab of palivizumab. In another embodiment, such an antibody comprises a VH or VL domain that is different from the VH or VL domain of palivizumab. In preferred embodiment, the  $T_m$  of the Fab fragment is at least about 90 °C or at least about 93 °C. In another preferred embodiment, the pI of the antibody is between about 8.5 to 9.5 or between about 9.0 to 9.5.

**[0029]** In another specific embodiment, the antibody comprises a VH domain of the antibody A4B4L1FR-S28R (SEQ ID NO:48). In still another embodiment, the antibody comprises a VL domain of the antibody A4B4L1FR-S28R (SEQ ID NO:11). In still another embodiment, said Fab is the Fab of antibody A4B4L1FR-S28R.

**[0030]** The invention also provides an antibody formulation comprising the above described antibody, said formulation having a viscosity of less than 10.00 cP at any temperature in the range of 1 to 26 °C.

[0031] The invention also provides an antibody formulation comprising the above described antibody, said formulation having an aggregation rate of less than 15% per day at any temperature in the range of 38 to 42 °C.

[0032] The invention also provides a method of preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a subject, e.g., otitis media, asthma, and wheezing, said method comprising administering a prophylactically or therapeutically effective amount of an antibody formulation comprising such antibody. In one embodiment, the formulation is administered parenterally, intramuscularly, intravenously, subcutaneously or intranasally.

[0033] The invention also provides an antibody formulation comprising a full length IgG<sub>1</sub> antibody, which immunospecifically binds to an RSV antigen, said formulation having a viscosity of less than 10.00 cP at any temperature in the range of 1 to 26 °C. The invention also provides an antibody formulation comprising any such antibody, said formulation having an aggregation rate of less than 15% per day at any temperature in the range of 38 to 42 °C. In one embodiment, the antibody is not palivizumab. In another embodiment, the antibody is not any of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and A17h4.

### 3.1 TERMINOLOGY

[0034] In the context of a polypeptide, the term “analog” as used herein refers to a polypeptide that possesses a similar or identical function as a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody but does not necessarily comprise a similar or identical amino acid sequence of a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody, or possess a similar or identical structure of a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody. A polypeptide that has a similar amino acid sequence refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide having an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody described herein; (b) a polypeptide encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody described herein of at least 5

amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the nucleotide sequence encoding a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody described herein. A polypeptide with similar structure to a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a RSV polypeptide, a fragment of a RSV, or an antibody described herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

**[0035]** To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical overlapping positions/total number of positions X 100%). In one embodiment, the two sequences are the same length.

**[0036]** The determination of percent identity between two sequences can also be accomplished using a mathematical algorithm. A preferred, non limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters



set, *e.g.*, for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the present invention. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.*, to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule of the present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, Nucleic Acids Res. 25:3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (see, *e.g.*, <http://www.ncbi.nlm.nih.gov>). Another preferred, non limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

**[0037]** The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

**[0038]** The terms “antibodies that immunospecifically bind to a RSV antigen” and analogous terms as used herein refers to antibodies that specifically bind to a RSV polypeptide or a fragment of a RSV polypeptide and do not non-specifically bind to other polypeptides. Antibodies that immunospecifically bind to a RSV polypeptide or fragment thereof may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to a RSV polypeptide or fragment thereof do not cross-react with other antigens. Antibodies that immunospecifically bind to a RSV polypeptide can be identified, for example, by immunoassays or other techniques known to those of skill in the art.

**[0039]** Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (*e.g.*, including monospecific and bi-specific, etc.), Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. In particular, antibodies of the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin

molecules, *i.e.*, molecules that contain an antigen-binding site that immunospecifically binds to a RSV antigen (preferably, a RSV F antigen) (*e.g.*, one or more complementarity determining regions (CDRs) of an anti-RSV antibody). The antibodies of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or a subclass of immunoglobulin molecule.

**[0040]** As used herein, the term “analogue” in the context of a non-proteinaceous analog refers to a second organic or inorganic molecule which possess a similar or identical function as a first organic or inorganic molecule and is structurally similar to the first organic or inorganic molecule.

**[0041]** The term “antibody fragment” as used herein refers to a fragment of an antibody that immunospecifically binds to a RSV antigen. Antibody fragments may be generated by any technique known to one of skill in the art and by proteolytic or non-proteolytic cleavage. For example, Fab and F(ab')<sub>2</sub> fragments may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the complete light chain, and the variable region, the CH1 region and the hinge region of the heavy chain. Antibody fragments can be also produced by recombinant DNA technologies. Antibody fragments may be one or more complementarity determining regions (CDRs) of antibodies.

**[0042]** The term “antibody type I fragment” as used herein refers to a multimeric protein comprising a full length antibody light chain, a full length antibody heavy chain and a C-terminal portion of an antibody heavy chain that, in human IgG<sub>1</sub> immunoglobulins, has an N-terminus at cysteine 223, aspartic acid 224, lysine 225, threonine 226, histidine 227, threonine 228 or cysteine 229 and a C-terminus at lysine 449. Amino acid numbering for the constant domain is given according to the Kabat EU numbering scheme (Kabat, E. A., T. T. Wu, H. M. Perry, K. S. Gottesman, and Foeller. 1991. Sequences of Proteins of Immunological Interest, U.S. Public Health Service, National Institutes of Health, Washington, D.C., which is incorporated herein by reference), unless otherwise indicated. In a specific embodiment, the full length antibody light chain, full length antibody heavy chain and C-terminal portion of an antibody heavy chain are linked by disulfide bonds as depicted in FIG. 14. In another specific embodiment, the type I fragment is capable of immunospecifically binding to an antigen of interest.

**[0043]** The term “antibody type II fragment” as used herein refers to a peptide, polypeptide, or protein comprising an antibody light chain and an N-terminal portion of an antibody heavy chain that, in human IgG<sub>1</sub> immunoglobulins, has a C-terminus at serine 222, cysteine 223, aspartic acid 224, lysine 225, threonine 226, histidine 227 or threonine 228 and an N-terminus at glycine 1. In a specific embodiment, the full length antibody light chain and N-terminal portion of an antibody heavy chain are linked by disulfide bonds as depicted in FIG. 14. In another specific embodiment, the type II fragment is capable of immunospecifically binding to an antigen of interest.

**[0044]** In the context of a polypeptide, the term “derivative” as used herein refers to a polypeptide that comprises an amino acid sequence of a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody that immunospecifically binds to a RSV polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term “derivative” as used herein also refers to a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody that immunospecifically binds to a RSV polypeptide which has been modified, *i.e.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody may be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a RSV polypeptide, a fragment of a RSV polypeptide, or an antibody described herein.

**[0045]** As used herein, the term “derivative” in the context of a non-proteinaceous derivative refers to a second organic or inorganic molecule that is formed based upon the structure of a first organic or inorganic molecule. A derivative of an organic molecule includes, but is not limited to, a molecule modified, *e.g.*, by the addition or deletion of a hydroxyl, methyl, ethyl, carboxyl or amine group. An organic molecule may also be esterified, alkylated and/or phosphorylated.

**[0046]** The term “effective amount” as used herein refers to the amount of a therapy (*e.g.*, an antibody of the invention) which is sufficient to reduce and/or ameliorate the severity

and/or duration of a disease or disorder. For example, the “effective amount” of an anti RSV antibody is that which is sufficient to reduce and/or ameliorate the severity and/or duration of an upper and/or lower respiratory tract RSV infection, otitis media, and/or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof), prevent the advancement or progression of the upper and/or lower respiratory tract RSV infection, otitis media and/or a symptom or respiratory condition relating thereto (*e.g.*, prevent the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection), prevent the recurrence, development, or onset of an upper and/or lower respiratory tract RSV infection, otitis media, and/or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof), and/or enhance/improve the prophylactic or therapeutic effect(s) of another therapy (*e.g.*, a therapy other than an antibody of the invention). Non-limiting examples of effective amounts of an antibody of the invention are provided in Section 5.3, *infra*. With respect to the treatment of a RSV infection, a therapeutically effective amount refers to the amount of a therapeutic agent sufficient to reduce or inhibit the replication of a virus, inhibit or reduce the infection of cell with the virus, inhibit or reduce the production of the viral particles, inhibit or reduce the release of viral particles, inhibit or reduce the spread of the virus to other tissues or subjects, or ameliorate one or more symptoms associated with the infection. In a specific embodiment, a therapeutically effective amount of a therapeutic agent reduces one or more of the following steps of a RSV life cycle: the docking of the virus particle to a cell, the introduction of viral genetic information into a cell, the expression of viral proteins, the production of new virus particles and the release of virus particles from a cell by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%. In another specific embodiment, a therapeutically effective amount of a therapeutic agent reduces the replication, multiplication or spread of a virus by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

[0047] The term “effective neutralizing titer” of an anti-RSV antibody as used herein refers to the amount of antibody which corresponds to the amount present in the serum of animals (human or cotton rat) that has been shown to be either clinically efficacious (in humans)

or to reduce virus by 99% in, for example, cotton rats. The 99% reduction is defined by a specific challenge of, *e.g.*,  $10^3$  pfu,  $10^4$  pfu,  $10^5$  pfu,  $10^6$  pfu,  $10^7$  pfu,  $10^8$  pfu, or  $10^9$  pfu of RSV.

**[0048]** The term “elderly” as used herein refers to a human subject who is age 65 or older.

**[0049]** The term “epitopes” as used herein refers to fragments of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. An epitope having immunogenic activity is a fragment of a polypeptide that elicits an antibody response in an animal. An epitope having antigenic activity is a fragment of a polypeptide to which an antibody immunospecifically binds as determined by any method well known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

**[0050]** The term “excipients” as used herein refers to inert substances which are commonly used as a diluent, vehicle, preservatives, binders, or stabilizing agent for drugs and includes, but not limited to, proteins (*e.g.*, serum albumin, etc.), amino acids (*e.g.*, aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, etc.), fatty acids and phospholipids (*e.g.*, alkyl sulfonates, caprylate, etc.), surfactants (*e.g.*, SDS, polysorbate, nonionic surfactant, etc.), saccharides (*e.g.*, sucrose, maltose, trehalose, etc.) and polyols (*e.g.*, mannitol, sorbitol, etc.). Also see Remington’s Pharmaceutical Sciences (by Joseph P. Remington, 18th ed., Mack Publishing Co., Easton, PA), which is hereby incorporated in its entirety.

**[0051]** The term “fragment” as used herein refers to a peptide or polypeptide comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino acid residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least contiguous 100 amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, or at least 250 contiguous amino acid residues of the amino acid sequence of a polypeptide or an antibody that immunospecifically binds to a polypeptide. In a specific embodiment, a fragment of a polypeptide or an antibody of that immunospecifically binds to an antigen retains at least 1, at least 2, or at least 3 functions of the polypeptide or antibody.

[0052] The term “fusion protein” as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (*i.e.*, a polypeptide or protein not normally a part of the antibody (*e.g.*, a non-anti-RSV antigen antibody)).

[0053] The terms “high concentration” and “concentrated antibody” as used herein refer to a concentration of 50 mg/ml or higher, preferably 95 mg/ml or higher of an antibody or antigen-binding fragment thereof in an antibody formulation.

[0054] The term “high potency” as used herein refers to antibodies that exhibit high potency as determined in various assays for biological activity (*e.g.*, neutralization of RSV) such as those described herein. For example, high potency antibodies of the invention have an  $IC_{50}$  value less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, less than 1.75 nM, less than 1.5 nM, less than 1.25 nM, less than 1 nM, less than 0.75 nM, less than 0.5 nM, less than 0.25 nM, less than 0.1 nM, less than 0.05 nM, less than 0.025 nM, or less than 0.01 nM, as measured by a microneutralization assay described herein. Further, high potency anti-RSV antibodies of the invention result in at least a 75%, preferably at least a 95% and more preferably a 99% lower RSV titer in a cotton rat 5 days after challenge with  $10^5$  pfu relative to a cotton rat not administered said antibodies. In certain embodiments of the invention, high potency anti-RSV antibodies of the present invention exhibit a high affinity and/or high avidity for one or more RSV antigens (*e.g.*, antibodies having an affinity of at least  $2 \times 10^8 M^{-1}$ , preferably at least  $2.5 \times 10^8 M^{-1}$ , at least  $5 \times 10^8 M^{-1}$ , at least  $10^9 M^{-1}$ , at least  $5 \times 10^9 M^{-1}$ , at least  $10^{10} M^{-1}$ , at least  $5 \times 10^{10} M^{-1}$ , at least  $10^{11} M^{-1}$ , at least  $5 \times 10^{11} M^{-1}$ , at least  $10^{12} M^{-1}$ , or at least  $5 \times 10^{12} M^{-1}$  for one or more RSV antigens).

[0055] The term “host” as used herein refers to an animal, preferably a mammal, and most preferably a human.

[0056] The term “host cell” as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0057] The term “human infant” as used herein refers to a human less than 24 months, preferably less than 16 months, less than 12 months, less than 6 months, less than 3 months, less than 2 months, or less than 1 month of age.

**[0058]** The term “human infant born prematurely” as used herein refers to a human born at less than 40 weeks gestational age, preferably less than 35 weeks gestational age, who is less than 6 months old, preferably less than 3 months old, more preferably less than 2 months old, and most preferably less than 1 month old.

**[0059]** As used herein, the term “in combination” refers to the use of more than one therapy. The use of the term “in combination” does not restrict the order in which therapies are administered to a subject with an infection. A first therapy can be administered before (*e.g.*, 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks), concurrently, or after (*e.g.*, 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks) the administration of a second therapy to a subject which had, has, or is susceptible to a disease or disorder. Any additional therapy can be administered in any order with the other additional therapies. In certain embodiments, the antibodies of the invention can be administered in combination with one or more non-antibody therapies. Non-limiting examples of therapies that can be administered in combination with an antibody of the invention include analgesic agents, anesthetic agents, antibiotics, or immunomodulatory agents.

**[0060]** As used herein, the term “infection” refers to all stages of RSV’s life cycle in a host (including, but not limited to the invasion by and replication of RSV in a cell or body tissue), and the pathological state resulting from the invasion by and replication of a RSV. The invasion by and multiplication of a RSV includes, but is not limited to, the following steps: the docking of the RSV particle to a cell, the introduction of viral genetic information into a cell, the expression of RSV proteins, the production of new RSV particles and the release of RSV particles from a cell.

**[0061]** The term “inorganic salt” as used herein refers to any compounds containing no carbon that result from replacement of part or all of the acid hydrogen or an acid by a metal or a group acting like a metal and are often used as a tonicity adjusting compound in pharmaceutical compositions and preparations of biological materials. The most common inorganic salts are NaCl, KCl, NaH<sub>2</sub>PO<sub>4</sub>, etc.

**[0062]** An “isolated” or “purified” antibody is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or

substantially free of chemical precursors or other chemicals when chemically synthesized. The language “substantially free of cellular material” includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a “contaminating protein”). When the antibody is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the antibody have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a preferred embodiment, antibodies of the invention are isolated or purified.

**[0063]** An “isolated” nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Moreover, an “isolated” nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a specific embodiment, a nucleic acid molecule(s) encoding an antibody of the invention is isolated or purified.

**[0064]** The phrase “low to undetectable levels of aggregation” as used herein refers to samples containing no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1% and most preferably no more than 0.5% aggregation by weight of protein as measured by high performance size exclusion chromatography (HPSEC) or by a multi-sizer.

**[0065]** The term “low to undetectable levels of fragmentation” as used herein refers to samples containing equal to or more than 95%, 98%, 99%, 99.5% or 99.9% of the total protein, for example, as determined by AUC or LC-MS.

**[0066]** The term “lower respiratory” tract refers to the major passages and structures of the lower respiratory tract including the windpipe (trachea) and the lungs, including the bronchi, bronchioles, and alveoli of the lungs.



[0067] As used herein, the term “low tolerance” refers to a state in which the patient suffers from side effects from a therapy so that the patient does not benefit from and/or will not continue therapy because of the adverse effects and/or the harm from side effects outweighs the benefit of the therapy.

[0068] As used herein, the terms “manage”, “managing” and “management” refer to the beneficial effects that a subject derives from a therapy (*e.g.*, a prophylactic or therapeutic agent), which does not result in a cure of the infection. In certain embodiments, a subject is administered one or more therapies (*e.g.*, prophylactic or therapeutic agents) to “manage” a infection, one or more symptoms thereof, or a respiratory condition associated with, potentiated by, or potentiating a RSV infection, so as to prevent the progression or worsening of the infection.

[0069] The terms “non-responsive” and “refractory” as used herein describe patients treated with a currently available therapy (such as but not limited to, a prophylactic or therapeutic agent) for a RSV infection, one or more symptoms thereof, or a respiratory condition associated with, potentiated by, or potentiating a RSV infection, which is not clinically adequate to relieve one or more symptoms associated with the infection. Typically, such patients suffer from severe, persistently active infection and require additional therapy to ameliorate the symptoms associated with their infection or respiratory condition.

[0070] As used herein, the terms “nucleic acids” and “nucleotide sequences” include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), combinations of DNA and RNA molecules or hybrid DNA/RNA molecules, and analogues of DNA or RNA molecules. Such analogues can be generated using, for example, nucleotide analogues, which include, but are not limited to, inosine or tritylated bases. Such analogues can also comprise DNA or RNA molecules comprising modified backbones that lend beneficial attributes to the molecules such as, for example, nuclease resistance or an increased ability to cross cellular membranes. The nucleic acids or nucleotide sequences can be single-stranded, double-stranded, may contain both single-stranded and double-stranded portions, and may contain triple-stranded portions, but preferably is double-stranded DNA.

[0071] The term “pharmaceutically acceptable” as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopia, European Pharmacopia or other generally recognized pharmacopia for use in animals, and more particularly in humans.

[0072] The term “polyol” as used herein refers to a sugar that contains many -OH groups compared to a normal saccharide.

[0073] As used herein, the terms “prevent,” “preventing,” and “prevention” refer to the prevention or inhibition of the development or onset of a disease or disorder, such as an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto in a subject, the prevention or inhibition of the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto resulting from the administration of a therapy (*e.g.*, a prophylactic or therapeutic agent), the prevention of a symptom of an upper and/or lower tract RSV infection, otitis media or a respiratory condition related thereto, or the administration of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents).

[0074] As used herein, the term “prophylactic agent” refers to any agent that can prevent the recurrence, spread or onset of a disease or disorder, such as an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof), and/or prevent the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection or otitis media. In certain embodiments, the term “prophylactic agent” refers to an antibody of the invention. In certain other embodiments, the term “prophylactic agent” refers to an agent other than an antibody of the invention. Preferably, a prophylactic agent is an agent which is known to be useful to or has been or is currently being used to prevent or impede the onset, development, progression and/or severity of a RSV infection (preferably an upper and/or lower respiratory tract RSV infection) otitis media, and/or a symptom or respiratory condition related thereto.

[0075] In certain embodiments of the invention, a “prophylactically effective serum titer” is the serum titer in a subject, preferably a human, that reduces the incidence of an upper and/or lower respiratory tract RSV infection, otitis media and/or a symptom or respiratory condition related thereto in said subject. In some embodiments, the prophylactically effective serum titer prevents the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection or otitis media. Preferably, the prophylactically effective serum titer reduces the incidence of RSV infections in humans with the greatest probability of complications resulting from RSV infection (*e.g.*, a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, a human who has had a bone marrow transplant, a human infant, or an

elderly human). In certain other embodiments of the invention, a “prophylactically effective serum titer” is the serum titer in a cotton rat that results in a RSV titer 5 days after challenge with  $10^5$  pfu that is 99% lower than the RSV titer 5 days after challenge with  $10^5$  pfu of RSV in a cotton rat not administered an antibody that immunospecifically binds to a RSV antigen.

[0076] As used herein, the term “refractory” refers to an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto that is not responsive to one or more therapies (*e.g.*, currently available therapies). In a certain embodiment, an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto is refractory to a therapy means that at least some significant portion of the symptoms associated with said upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto are not eliminated or lessened by that therapy. The determination of whether an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto is refractory can be made either *in vivo* or *in vitro* by any method known in the art for assaying the effectiveness of therapy for the infection, otitis media or the respiratory condition related thereto.

[0077] The term “RSV antigen” refers to a RSV polypeptide to which an antibody immunospecifically binds. A RSV antigen also refers to an analog or derivative of a RSV polypeptide or fragment thereof to which an antibody immunospecifically binds.

[0078] The term “serum titer” as used herein refers to an average serum titer in a population of least 10, preferably at least 20, and most preferably at least 40 subjects.

[0079] The term “saccharide” as used herein refers to a class of molecules that are derivatives of polyhydric alcohols. Saccharides are commonly referred to as carbohydrates and may contain different amounts of sugar (saccharide) units, *e.g.*, monosaccharides, disaccharides and polysaccharides.

[0080] As used herein, the term “side effects” encompasses unwanted and adverse effects of a therapy (*e.g.*, a prophylactic or therapeutic agent). Adverse effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapy (*e.g.*, a prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Examples of side effects include, but are not limited to, nausea, vomiting, anorexia, abdominal cramping, fever, pain, loss of body weight, dehydration, alopecia, dyspnea, insomnia, dizziness, mucositis, nerve and muscle effects, fatigue, dry mouth, and loss of appetite, rashes or swellings at the site of administration, flu-like symptoms such as fever, chills and fatigue, digestive tract

problems and allergic reactions. Additional undesired effects experienced by patients are numerous and known in the art. Many are described in the Physician's Desk Reference (58<sup>th</sup> ed., 2004).

**[0081]** The terms "stability" and "stable" as used herein in the context of a formulation comprising an antibody or antigen-binding fragment refer to the resistance of the antibody or antibody fragment in the formulation to thermal and chemical unfolding, aggregation, degradation or fragmentation under given manufacture, preparation, transportation and storage conditions. The "stable" formulations of the invention retain biological activity equal to or more than 80%, 85%, 90%, 95%, 98%, 99%, 99.5%, or 99.9% under given manufacture, preparation, transportation and storage conditions. The stability of the antibody or antibody fragment can be assessed by degrees of aggregation, degradation or fragmentation or levels of particular fragments (e.g., Fragment Type I or Fragment Type II) or types or sizes of aggregates by methods known to those skilled in the art, including but not limited to reduced AUC, SEC, LC-MS, particle multisizer Capillary Gel Electrophoresis (rCGE), Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) and HPSEC, compared to a reference, for example, a commercially available lyophilized palivizumab reconstituted to 100 mg/ml in 50 mM histidine/3.2 mM glycine buffer with 6% mannitol at pH 6.0. The reference regularly gives a single peak ( $\geq 97\%$  area) by HPSEC. The overall stability of a formulation comprising an antibody or fragment thereof that immunospecifically binds to a RSV antigen can be assessed by various immunological assays including, for example, ELISA and radioimmunoassay, using the specific epitope of RSV.

**[0082]** As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, a subject is preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats, etc.) and a primate (e.g., monkey and human), most preferably a human. In one embodiment, the subject is a mammal, preferably a human, with an upper and/or lower respiratory tract RSV infection or otitis media. In another embodiment, the subject is a mammal, preferably a human, at risk of developing an upper and/or lower respiratory tract RSV infection or otitis media (e.g., an immunocompromised or immunosuppressed mammal, or a genetically predisposed mammal). In one embodiment, the subject is a human with a respiratory condition (including, but not limited to asthma, wheezing or RAD) that stems from, is caused by or associated with a RSV infection.

**[0083]** As used herein, the term "palivizumab standard reference" or analogous terms refer to commercially available lyophilized palivizumab, as described in the Physicians' Desk

Reference, 56<sup>th</sup> edition, 2002. Reconstituted palivizumab may contain, *e.g.*, the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% manitol and the active ingredient, the antibody, at a concentration of 100 milligrams per ml solution.

**[0084]** As used herein, the terms “subject” and “patient” are used interchangeably. As used herein, the terms “subject” and “subjects” refer to an animal, preferably a mammal including a non-primate (*e.g.*, a cow, pig, horse, cat, dog, rat, and mouse) and a non-primate (*e.g.*, a monkey such as a cynomolgous monkey and a human), and more preferably a human.

**[0085]** The term “substantially free of surfactant” as used herein refers to a formulation of an antibody or fragment thereof that immunospecifically binds to a RSV antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants and/or less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants.

**[0086]** The term “substantially free of salt” as used herein refers to a formulation of an antibody or fragment thereof that immunospecifically binds to a RSV antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of inorganic salts.

**[0087]** The term “surfactant” as used herein refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and nonionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

**[0088]** The term “synergistic” as used herein refers to a combination of therapies (*e.g.*, use of prophylactic or therapeutic agents) which is more effective than the additive effects of any two or more single therapy. For example, a synergistic effect of a combination of prophylactic or therapeutic agents permits the use of lower dosages of one or more of the agents and/or less frequent administration of said agents to a subject with a RSV infection. The ability to utilize lower dosages of prophylactic or therapeutic therapies and/or to administer said therapies less frequently reduces the toxicity associated with the administration of said therapies to a subject without reducing the efficacy of said therapies in the prevention, management or treatment of a RSV infection. In addition, a synergistic effect can result in improved efficacy of therapies in the prevention or treatment of a RSV infection. Finally, synergistic effect of a

combination of therapies (*e.g.*, prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of any single therapy.

[0089] As used herein, the term “therapeutic agent” refers to any agent that can be used in the treatment, management, prevention or amelioration of a disease or disorder, for example, an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto. In certain embodiments, the term “therapeutic agent” refers to an antibody of the invention. In certain other embodiments, the term “therapeutic agent” refers to an agent other than an antibody of the invention. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the prevention, treatment, management or amelioration of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media, or one or more symptoms or respiratory conditions related thereto.

[0090] In certain embodiments of the invention, a “therapeutically effective serum titer” is the serum titer in a subject, preferably a human, that reduces the severity, the duration and/or the symptoms associated with a RSV infection in said subject. Preferably, the therapeutically effective serum titer reduces the severity, the duration and/or the number symptoms associated with upper and/or lower respiratory tract RSV infections in humans with the greatest probability of complications resulting from the infection (*e.g.*, a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, a human who has had a bone marrow transplant, a human infant, or an elderly human). In certain other embodiments of the invention, a “therapeutically effective serum titer” is the serum titer in a cotton rat that results in a RSV titer 5 days after challenge with  $10^5$  pfu that is 99% lower than the RSV titer 5 days after challenge with  $10^5$  pfu of RSV in a cotton rat not administered an antibody that immunospecifically binds to a RSV antigen.

[0091] As used herein, the term “therapy” refers to any protocol, method and/or agent that can be used in the prevention, treatment or management of a disease or disorder, such as an RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). In certain embodiments, the terms “therapies” and “therapy” refer to a biological therapy, supportive therapy, and/or other therapies useful in the treatment, management, prevention and/or amelioration of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) known to one of skill in the art such as medical personnel.

[0092] As used herein, the terms “treat,” “treatment” and “treating” refer to the reduction or amelioration of the progression, severity, and/or duration of a disease or disorder, such as an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition related thereto (such as asthma, wheezing, RAD, or a combination thereof) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents). In specific embodiments, such terms refer to the reduction or inhibition of the replication of RSV, the inhibition or reduction in the spread of RSV to other tissues or subjects (*e.g.*, the spread to the lower respiratory tract), the inhibition or reduction of infection of a cell with a RSV, or the amelioration of one or more symptoms associated with an upper and/or lower respiratory tract RSV infection or otitis media.

[0093] The term “upper and/or lower respiratory” tract refers to the major passages and structures of the upper and/or lower respiratory tract including the nose or nostrils, nasal cavity, mouth, throat (pharynx), and voice box (larynx).

#### 4. DESCRIPTION OF THE FIGURES

[0094] FIG. 1 is a schematic diagram showing an outline for preparing purified antibodies that immunospecifically bind to RSV antigen.

[0095] FIG. 2 is a schematic diagram showing an outline for preparing purified antibodies that immunospecifically bind to RSV antigen.

[0096] FIG. 3A-3B show the amino acid sequences of the (A) light chain variable region and (B) heavy chain variable region of a monoclonal antibody that binds to a RSV antigen, the potency of which can be increased by methods described herein or in Applicants' copending applications Serial Nos. 60/168,426 and 60/186,252 and U.S. Patent No. 6,656,467. For reference purposes, this is the amino acid sequence of the palivizumab antibody disclosed in Johnson et al., 1997, J. Infect. Dis. 176:1215-1224 and U.S. Patent No. 5,824,307. Here, the CDR regions are underlined while non-underlined residues form the framework (FR) regions of the variable regions of the antibody. In this antibody, the CDRs are derived from a mouse antibody while the framework regions are derived from a human antibody. The constant regions (not shown) are also derived from a human antibody.

[0097] FIG. 4A-4B show the (A) light chain variable region and (B) heavy light chain variable region for an antibody sequence. CDR regions are underlined, and the non-underlined

residues form the framework of the variable regions of the antibody. This sequence differs from the sequence disclosed in Figures 1A-1B in the first 4 residues of VH CDR1 of the light chain, residue 103 of the light chain FR4 and residue 112 of the heavy chain FR4. For reference purposes, these VL and VH sequences are identical to the VL and VH domains of IX-493L1FR (see Table 2).

[0098] **FIG. 5A-5B** show the nucleotide and translated amino acid sequence of the A4B4L1FR-S28R (A) VH domain and (B) VL domain. CDR sequences are underlined. Where palivizumab differs from A4B4L1FR-S28R, the palivizumab amino acid is shown below the motavizumab sequence. Residues that were introduced on the IX-493L1FR template (see also Figure 2) are indicated in bold.

[0099] **FIG. 6A-6C.** Quantitation of aggregates, fragments and monomers of A4B4L1FR-S28R during storage at (♦) 2-8 °C, (□) 20-24 °C and (▲) 38-42 °C; as determined by SEC with UV detection. (A) Percent Aggregates; (B) Percent Fragments and (C) Percent Purity (monomers).

[00100] **FIG. 7.** Plot of Aggregation and fragmentation rates of A4B4L1FR-S28R based on the SEC data of FIGs. 19A-19C; (♦) rate of aggregation, (■) rate of fragmentation.

[00101] **FIG. 8.** SEC profile of A4B4L1FR-S28R formulated in 25 mM histidine-HCl, pH 6.0 after storage at 38-42 °C for one month.

[00102] **FIG. 9.** Comparison of AUC and SEC analysis of A4B4L1FR-S28R at initial, 9-month and 14-month time points. All samples were formulated in 25 mM histidine-HCl, pH 6.0 and, for the 9 and 14 month points, stored at 38-42 °C. (A) AUC; (B) SEC.

[00103] **FIG. 10.** Comparison of antibody sample concentration dependence of signal/noise ratio for AUC analysis.

[00104] **FIG. 11.** AUC analysis of A4B4L1FR-S28R formulated in 25 mM histidine-HCl, pH 6.0 and stored at 38-42 °C over the course of 5 days.

[00105] **FIG. 12.** LC-MS analysis of deglycosylated, reduced and alkylated antibody type I fragment. Sample collected from SEC of A4B4L1FR-S28R formulated in 25 mM histidine-HCl, pH 6.0 and stored at 38-42 °C for 1 month.



[00106] **FIG. 13.** LC-MS analysis of deglycosylated, reduced and alkylated antibody type II fragment. Sample collected from SEC of A4B4L1FR-S28R formulated in 25 mM histidine-HCl, pH 6.0 and stored at 38-42 °C for 1 month.

[00107] **FIG. 14A-14B** is a diagram showing the characteristic fragmentation pattern of A4B4L1FR-S28R, forming antibody type I and antibody type II fragments. **(A)** Cleavage sites within the hinge region of the antibody heavy chain. Bold arrows indicate preferred or predominant cleavage sites. **(B)** Schematic showing characteristics of antibody type I and antibody type II fragments. an outline for preparing purified antibodies that immunospecifically bind to RSV antigen. The antibody type I fragment comprises a full length antibody light chain, a full length antibody heavy chain and a C-terminal portion of an antibody heavy chain that, in human IgG<sub>1</sub> immunoglobulins, has an N-terminus at cysteine 223, aspartic acid 224, lysine 225, threonine 226, histidine 227, threonine 228 or cysteine 229. The antibody type II fragment comprises an antibody light chain and an N-terminal portion of an antibody heavy chain that, in human IgG<sub>1</sub> immunoglobulins, has a C-terminus at serine 222, cysteine 223, aspartic acid 224, lysine 225, threonine 226, histidine 227 or threonine 228.

[00108] **FIG. 15.** Chromatograms of Lys-C digested aggregates, monomers and fragments collected from SEC of A4B4L1FR-S28R formulated in 25 mM histidine-HCl, pH 6.0 and stored at 38-42 °C for 1 month. The arrows point to the low level disulfide bond scrambling peaks.

[00109] **FIG. 16.** Chromatograms of Lys-C digested aggregates with and without reduction. Samples were collected from SEC of A4B4L1FR-S28R formulated in 25 mM histidine-HCl, pH 6.0 and stored at 38-42 °C for 1 month. The arrows point to the low level disulfide bond scrambling peaks.

[00110] **FIG. 17** summarizes the results of a RSV microneutralization assay using the anti-RSV antibodies A4B4L1FR-S28R and palivizumab, comparing the ability of both antibodies to inhibit the *in vitro* replication of RSV (Long) in the assay.

[00111] **FIG. 18** summarizes the results of a RSV microneutralization assay demonstrating the ability of A4B4L1FR-S28R to inhibit the *in vitro* replication of RSV (Long) in the microneutralization assay.

[00112] **FIG. 19** DSC thermograms of the full length palivizumab (top panel) and an overlay of the thermograms obtained from purified Fab and Fc fragments of palivizumab (bottom panel).

Two discrete peaks are seen for the Fc domain at approximately 68°C and 83°C. A single peak is seen for the Fab fragment at approximately 87°C.

[00113] **FIG. 20** plot of the T<sub>m</sub> and pI values of palivizumab and motavizumab.

[00114] **FIG.21** plot of the viscosity of a 100 mg/ml solution of palivizumab and motavizumab at a range of temperatures from about 2 to 25 °C.

[00115] **FIG. 22** plot of the aggregation rates of palivizumab and motavizumab against the Fab T<sub>m</sub> for each antibody.

## 5. DETAILED DESCRIPTION OF THE INVENTION

### 5.1 Methods of Preparing Antibody Formulations

[00116] The present invention provides methods for preparing formulations of antibodies, or derivatives, analogues, or fragments thereof that immunospecifically bind to a an antigen of interest. Such antibodies may be purified according to any method known in the art for purification of antibodies. FIGS. 1 and 2 are schematic diagrams showing alternate outlines for preparing purified antibodies. In one embodiment, the methods for preparing liquid formulations of the present invention comprise: concentrating a fraction containing the purified antibody or a fragment to a final antibody or fragment concentration of from about 15 mg/ml, about 20 mg/ml, about 30 mg/ml, about 40 mg/ml, about 50 mg/ml, about 60 mg/ml, about 70 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 110 mg/ml, about 125 mg/ml, about 150 mg/ml, about 200 mg/ml, about 250 mg/ml, or about 300 mg/ml using a semipermeable membrane with an appropriate molecular weight (MW) cutoff (*e.g.*, 30 kD cutoff for whole antibody molecules and F(ab')<sub>2</sub> fragments; and 10 kD cutoff for antibody fragments, such as Fab fragments) and difiltrating the concentrated antibody fraction into the formulation buffer using the same membrane. Antibodies are preferably expressed in myeloma cells, more preferably murine myeloma cells, most preferably NSO cells.

[00117] In the embodiment outlined by FIG. 1, conditioned medium containing antibody or a fragment thereof that immunospecifically binds to an antigen of interest is subjected to CUNO filtration and the filtered antibody is subjected to HS50 cation exchange chromatography. The fraction from the HS50 cation exchange chromatography is then subjected to rProtein A affinity chromatography followed by low pH treatment. Following low pH treatment, the antibody fraction is subject to super Q 650 anion exchange chromatography and then nanofiltration. The fraction of the antibody obtained after nanofiltration is then subjected to diafiltration to concentrate the antibody fraction into the formulation buffer using the same membrane.

**[00118]** Using the embodiment of FIG. 2, conditioned medium containing antibody or a fragment thereof that immunospecifically binds to an antigen of interest is subjected to CUNO filtration and the filtered antibody is subjected to Fractogel® S cation exchange chromatography. The fraction from the cation exchange chromatography is then subjected to super Q anion chromatography, followed by nanofiltration with a Planova® 20 N nanofilter. The antibody fraction recovered after nanofiltration is then subjected to low pH treatment followed by hydroxyapatite (HA) chromatography. The fraction of the antibody obtained after HA chromatography is then subjected to diafiltration to concentrate the antibody fraction into the formulation buffer using the same membrane.

**[00119]** The formulation buffer of the present invention preferably comprises histidine at a concentration ranging from about 1 mM to about 100 mM, about 10 mM to about 50 mM, about 20 mM to about 30 mM, or about 23 mM to about 27 mM. Preferably, the formulation buffer of the present invention comprises histidine at a concentration of about 25 mM. The formulations may further comprise glycine at a concentration of less than 100 mM, less than 50 mM, less than 3.0 mM, less than 2.0 mM, or less than 1.8 mM. Preferably, the formulations comprise glycine at a concentration of 1.6 mM. The amount of glycine in the formulation should not cause a significant buffering in order to avoid antibody precipitation at its isoelectric point. The pH of the formulation may range from about 5.0 to about 7.0, preferably about 5.5 to about 6.5, more preferably about 5.8 to about 6.2, and most preferably about 6.0. To obtain an appropriate pH for a particular antibody, it is preferable that histidine (and glycine, if added) is first dissolved in water to obtain a buffer solution with higher pH than the desired pH and then the pH is brought down to the desired level by adding HCl. This way, the formation of inorganic salts (*e.g.*, formation of NaCl when, for example, histidine hydrochloride is used as histidine and pH is raised to a desired level by adding NaOH) can be avoided.

**[00120]** The formulations of the present invention can be prepared as unit dosage forms by preparing a vial containing an aliquot of the liquid formulation for a one-time use. For example, a unit dosage per vial may contain 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml of different concentrations of an antibody or a fragment thereof that immunospecifically binds to the antigen of interest ranging from about 15 mg/ml to about 300 mg/ml. If necessary, these preparations can be adjusted to a desired concentration by adding a sterile diluent to each vial.

**[00121]** The formulations of the present invention may be sterilized by various sterilization methods, including sterile filtration, radiation, etc. In a most preferred embodiment,

the difiltrated antibody formulation is filter-sterilized with a presterilized 0.22-micron filter. In specific embodiments, sterilized liquid formulations of the present invention may be administered to a subject to prevent, treat, manage or ameliorate a RSV infection, one or more symptoms thereof, or a respiratory condition associated with, potentiated by, potentiating a RSV infection.

**[00122]** The formulations of the invention comprise labeled antibodies, derivatives and analogues thereof, that immunospecifically bind to an antigen of interest and can be used for diagnostic purposes to detect, diagnose, or monitor a disorder associated with and/or characterized by the presence or said antigen. In a specific embodiment, the formulations of the invention comprise labeled antibodies, derivatives and analogues thereof, that immunospecifically bind to a RSV antigen and can be used for diagnostic purposes to detect, diagnose, or monitor a RSV infection.

**[00123]** The invention encompasses both liquid and lyophilized forms of the formulations. Methods to produce lyophilized forms of liquid formulations are well-characterized in the art. In one embodiment, the ingredients of formulation of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

**[00124]** The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

**[00125]** The formulation of the invention can be further processed into an oral or non-oral dosage form, for immediate or extended release. The formulation can additionally comprise inactive ingredients ordinarily used in pharmaceutical preparation such as diluents, fillers, disintegrants, sweeteners, lubricants and flavors. The formulation may also be processed for intravenous administration, either by bolus injection or sustained drip, or for release from an

implanted capsule. A typical formulation for intravenous administration utilizes physiological saline as a diluent.

## **5.2 Formulations of Antibodies**

**[00126]** The invention provides formulations comprising antibodies of the invention for use in diagnosing, detecting, or monitoring a disorder, in preventing, treating, managing, or ameliorating of a disorder or one or more symptoms thereof, and/or in research. In a specific embodiment, the formulation of the invention comprises one or more antibodies. In another embodiment, the formulation of the invention comprises one or more antibodies and one or more prophylactic or therapeutic agents other than antibodies. Preferably, the prophylactic or therapeutic agents known to be useful for or having been or currently being used in the prevention, treatment, management, or amelioration of a disorder or one or more symptoms thereof. In accordance with these embodiments, the composition may further comprise of a carrier, diluent or excipient.

**[00127]** The formulations of the present invention provide antibody formulations which are substantially free of surfactant, inorganic salts, and/or other excipients and yet exhibit high stability during long periods of storage. In a specific embodiment, such antibody formulations are homogeneous. The formulations of the present invention comprise histidine at concentrations between 1 and 100 mM and an antibody which immunospecifically binds to a antigen of interest at concentrations of about 15 mg/ml to about 300 mg/ml. In one embodiment, the formulations of the invention do not comprise other ingredients except for water or suitable solvents. In a specific embodiment, the antibody immunospecifically binds to an RSV antigen and in preferred embodiments is not palivizumab or a fragment thereof.

**[00128]** In one embodiment, the antibody of the formulation of the invention is an antibody or antibody fragment conjugated to another moiety, including, but not limited to, a heterologous polypeptide, another antibody or another fragment, a marker sequence, a diagnostic agent, a therapeutic agent, a radioactive metal ion, a polymer, albumin, and a solid support. In another embodiment, formulations of the invention comprise two or more antibodies, or fragments thereof that immunospecifically binds to an antigen of interest. In a specific embodiment, formulations of the invention comprise two or more antibodies, or fragments thereof, that immunospecifically binds to a RSV antigen, wherein at least one of the antibodies or antibody fragments is not palivizumab or a fragment thereof.

**[00129]** The concentration of an antibody or a fragment thereof which is included in the formulations of the invention is at least 15 mg/ml, at least 20 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 35 mg/ml, at least 40 mg/ml, at least 45 mg/ml, at least 50 mg/ml, at least 55 mg/ml, at least 60 mg/ml, at least 65 mg/ml, at least 70 mg/ml, at least 75 mg/ml, at least 80 mg/ml, at least 85 mg/ml, at least 90 mg/ml, at least 95 mg/ml, at least 100 mg/ml, at least 105 mg/ml, at least 110 mg/ml, at least 115 mg/ml, at least 120 mg/ml, at least 125 mg/ml, at least 130 mg/ml, at least 135 mg/ml, at least 140 mg/ml, at least 150 mg/ml, at least 200 mg/ml, at least 250 mg/ml, or at least 300 mg/ml.

**[00130]** The concentration of histidine which is included in the formulations of the invention ranges from about 1 mM to about 100 mM, about 10 mM to about 50 mM, about 20 mM to about 30 mM, or about 23 mM to about 27 mM, and is most preferably about 25 mM. Histidine can be in the form of L-histidine, D-histidine, or a mixture thereof, but L-histidine is the most preferable. Histidine can also be in the form of hydrates. Histidine may be used in a form of pharmaceutically acceptable salt, such as hydrochloride (*e.g.*, monohydrochloride and dihydrochloride), hydrobromide, sulfate, acetate, etc. The purity of histidine should be at least 98%, preferably at least 99%, and most preferably at least 99.5%.

**[00131]** The pH of the formulation should not be equal to the isoelectric point of the particular antibody to be used in the formulation and may range from about 5.0 to about 7, preferably about 5.5 to about 6.5, more preferably about 5.8 to about 6.2, and most preferably about 6.0.

**[00132]** In addition to histidine and an antibody or a fragment thereof, the formulations of the present invention may further comprise glycine at a concentration of less than 100 mM, less than 50 mM, less than 3.0 mM, less than 2.0 mM, or less than 1.8 mM, and most preferably 1.6 mM. The amount of glycine in the formulation should not cause a significant buffering effect so that antibody precipitation at its isoelectric point can be avoided. Glycine may be also used in a form of pharmaceutically acceptable salt, such as hydrochloride, hydrobromide, sulfate, acetate, etc. The purity of glycine should be at least 98%, preferably at least 99%, and most preferably 99.5%. In a specific embodiment, glycine is included in the formulations of the present invention.

**[00133]** Optionally, the formulations of the present invention may further comprise other excipients, such as saccharides (*e.g.*, sucrose, mannose, trehalose, etc.) and polyols (*e.g.*, mannitol, sorbitol, etc.). In one embodiment, the other excipient is a saccharide. In a specific

embodiment, the saccharide is sucrose, which is at a concentration ranging from between about 1% to about 20%, preferably about 5% to about 15%, and more preferably about 8% to 10%. In another embodiment, the other excipient is a polyol. Preferably, however, the liquid formulations of the present invention do not contain mannitol. In a specific embodiment, the polyol is polysorbate (*e.g.*, Tween 20), which is at a concentration ranging from between about 0.001% to about 1%, preferably, about 0.01 to about 0.1.

**[00134]** The formulations of the present invention exhibit stability at the temperature ranges of 38°C-42°C for at least 60 days and, in some embodiments, at least 120 days, of 20°C-24°C for at least 1 year, of 2°C-8°C (in particular, at 4°C) for at least 3 years, at least 4 years, or at least 5 years and at -20°C for at least 3 years, at least 4 years, or at least 5 years, as assessed by AUC, LC-MS, size exclusion chromatography (SEC) or high performance size exclusion chromatography (HPSEC) or particle multisizer. Namely, the formulations of the present invention have low to undetectable levels of aggregation and/or fragmentation, as defined herein, after the storage for the defined periods as set forth above. Preferably, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, and most preferably no more than 0.5% (but in certain embodiments, at least 0.1%) of the antibody or antibody fragment forms an aggregate or fragment (particularly of fragment I or fragment II) as measured by AUC, LC-MS, SEC or HPSEC, after the storage for the defined periods as set forth above. Furthermore, formulations of the present invention exhibit almost no loss in biological activities of the antibody or antibody fragment during the prolonged storage under the condition described above, as assessed by various immunological assays including, but not limited to, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay to measure the ability of the antibody or antibody fragment to immunospecifically bind to an antigen of interest, and by a C3a/C4a assay to measure the complement activating ability of the antibody. The formulations of the present invention retain after the storage for the above-defined periods more than 80%, more than 85%, more than 90%, more than 95%, more than 98%, more than 99%, or more than 99.5% of the initial biological activities of the formulation prior to the storage.

**[00135]** The formulations of the present invention can be prepared as unit dosage forms. For example, a unit dosage per vial may contain 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml of different concentrations of an antibody or a fragment thereof that immunospecifically binds to a RSV antigen ranging from about 15 mg/ml to about 300 mg/ml. If necessary, these preparations can be adjusted to a desired concentration by adding a sterile diluent to each vial.

[00136] The invention encompasses stable liquid formulations comprising a single antibody or fragment thereof that immunospecifically binds to an antigen of interest. In a specific embodiment, the invention encompasses stable liquid formulations comprising a single antibody or fragment thereof that immunospecifically binds to a RSV antigen, with the proviso that said antibody is not palivizumab. The invention also encompasses stable liquid formulations comprising two or more antibodies or fragments thereof that immunospecifically bind to a RSV antigen. In one embodiment, a stable liquid formulation of the invention comprises two or more antibodies or fragments thereof that immunospecifically bind to a RSV antigen, wherein one of the antibodies or antibody fragments is not palivizumab or a fragment thereof.

### 5.3 Antibodies Useful in the Formulations of the Invention

[00137] The antibodies useful in the present invention include, but are not limited to, monoclonal antibodies, synthetic antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, single-chain Fvs (scFv) (including bi-specific scFvs), single chain antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), and epitope-binding fragments of any of the above. In particular, antibodies of the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds to an antigen. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or subclass of immunoglobulin molecule. Preferably, the antibodies of the invention are IgG, more preferably, IgG<sub>1</sub>.

[00138] The antibodies useful in the present invention may be from any animal origin including birds and mammals (*e.g.*, human, murine, donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken). Preferably, the antibodies are human or humanized monoclonal antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from mice or other animal that express antibodies from human genes.

[00139] The antibodies useful in the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may immunospecifically bind to different epitopes of a polypeptide or may immunospecifically bind to both a polypeptide as well a heterologous epitope, such as a heterologous polypeptide or solid support material. See,



*e.g.*, International Publication Nos. WO 93/17715, WO 92/08802, WO 91/00360, and WO 92/05793; Tutt, et al., 1991, *J. Immunol.* 147:60-69; U.S. Patent Nos. 4,474,893, 4,714,681, 4,925,648, 5,573,920, and 5,601,819; and Kostelny et al., 1992, *J. Immunol.* 148:1547-1553.

**[00140]** The antibodies useful in the present invention include derivatives of the antibodies. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding an antibody to be used with the methods of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In a preferred embodiment, the derivatives have conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

**[00141]** The antibodies useful in the present invention include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific

chemical cleavage, acetylation, formylation, synthesis in the presence of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[00142] Antibodies useful in the present invention or fragments thereof can also comprise a framework region known to those of skill in the art. In certain embodiments, one or more framework regions, preferably, all of the framework regions, of an antibody to be used in the methods of the invention or fragment thereof are human. In certain other embodiments of the invention, the fragment region of an antibody of the invention or fragment thereof is humanized. In certain embodiments, the antibody to be used with the methods of the invention is a synthetic antibody, a monoclonal antibody, an intrabody, a chimeric antibody, a human antibody, a humanized chimeric antibody, a humanized antibody, a glycosylated antibody, a multispecific antibody, a human antibody, a single-chain antibody, or a bispecific antibody.

[00143] In certain embodiments of the invention, the antibodies useful in the present invention have half-lives in a mammal, preferably a human, of greater than 12 hours, greater than 1 day, greater than 3 days, greater than 6 days, greater than 10 days, greater than 15 days, greater than 20 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. Antibodies or antigen-binding fragments thereof having increased *in vivo* half-lives can be generated by techniques known to those of skill in the art. For example, antibodies or antigen-binding fragments thereof with increased *in vivo* half-lives can be generated by modifying (*e.g.*, substituting, deleting or adding) amino acid residues identified as involved in the interaction between the Fc domain and the FcRn receptor (see, *e.g.*, PCT Publication No. WO 97/34631 and U.S. Patent Application No.: 10/020,354, entitled "Molecules with Extended Half-Lives, Compositions and Uses Thereof", filed December 12, 2001, by Johnson et al., which are incorporated herein by reference in their entireties). Such antibodies or antigen-binding fragments thereof can be tested for binding activity to RSV antigens as well as for *in vivo* efficacy using methods known to those skilled in the art, for example, by immunoassays described herein.

[00144] Further, antibodies or antigen-binding fragments thereof with increased *in vivo* half-lives can be generated by attaching to said antibodies or antibody fragments polymer molecules such as high molecular weight polyethyleneglycol (PEG). PEG can be attached to said antibodies or antibody fragments with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C- terminus of said antibodies or antibody fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer

derivatization that results in minimal loss of biological activity will be used. The degree of conjugation will be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by, *e.g.*, size exclusion or ion-exchange chromatography. PEG-derivatized antibodies or antigen-binding fragments thereof can be tested for binding activity to RSV antigens as well as for *in vivo* efficacy using methods known to those skilled in the art, for example, by immunoassays described herein.

[00145] The antibodies useful in the present invention can be single-chain antibodies. The design and construction of a single-chain antibody is described in Marasco et al, 1993, Proc Natl Acad Sci 90:7889-7893, which is incorporated herein by reference in its entirety.

[00146] In certain embodiments, the antibodies useful in the present invention bind to an intracellular epitope, *i.e.*, are intrabodies. An intrabody comprises at least a portion of an antibody that is capable of immunospecifically binding an antigen and preferably does not contain sequences coding for its secretion. Such antibodies will bind its antigen intracellularly. In one embodiment, the intrabody comprises a single-chain Fv ("sFv"). sFv are antibody fragments comprising the V<sub>H</sub> and V<sub>L</sub> domains of antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

[00147] In a further embodiment, the intrabody preferably does not encode an operable secretory sequence and thus remains within the cell (see generally Marasco, WA, 1998, "Intrabodies: Basic Research and Clinical Gene Therapy Applications" Springer:New York).

### 5.3.1 Antibody Conjugates

[00148] The present invention also encompasses formulations comprising antibodies that are conjugated or fused to one or more moieties, including but not limited to, peptides, polypeptides, proteins, fusion proteins, nucleic acid molecules, small molecules, mimetic agents, synthetic drugs, inorganic molecules, and organic molecules.

[00149] The present invention encompasses formulations comprising antibodies that are recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a

polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies may be used to target heterologous polypeptides to particular cell types, either in vitro or in vivo, by fusing or conjugating the antibodies to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to heterologous polypeptides may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., International publication No. WO 93/21232; European Patent No. EP 439,095; Naramura et al., 1994, Immunol. Lett. 39:91-99; U.S. Pat. No. 5,474,981; Gillies et al., 1992, PNAS 89:1428-1432; and Fell et al., 1991, J. Immunol. 146:2446-2452, which are incorporated by reference in their entireties.

**[00150]** The present invention further includes formulations comprising heterologous proteins, peptides or polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)<sub>2</sub> fragment, a VH domain, a VL domain, a VH CDR, a VL CDR, or fragment thereof. Methods for fusing or conjugating polypeptides to antibody portions are well-known in the art. See, e.g., U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166; International publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi et al., 1991, Proc. Natl. Acad. Sci. USA 88: 10535-10539; Zheng et al., 1995, J. Immunol. 154:5590-5600; and Vil et al., 1992, Proc. Natl. Acad. Sci. USA 89:11337-11341 (said references incorporated by reference in their entireties).

**[00151]** Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention or fragments thereof (e.g., antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson, et al., 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. One or more portions of a polynucleotide encoding an antibody or antibody

fragment may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

**[00152]** Moreover, the antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767) and the "flag" tag.

**[00153]** In other embodiments, antibodies useful in the present invention or fragments, analogs or derivatives thereof can be conjugated to a diagnostic or detectable agent. Such antibodies can be useful for monitoring or prognosing the development or progression of a disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can be accomplished by coupling the antibody to detectable substances including, but not limited to various enzymes, such as but not limited to horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as but not limited to streptavidin/biotin and avidin/biotin; fluorescent materials, such as but not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as but not limited to iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115}\text{In}$ ,  $^{113}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ , and  $^{117}\text{Te}$ ; positron emitting metals using various positron emission tomographies, norradioactive paramagnetic metal ions, and molecules that are radiolabelled or conjugated to specific radioisotopes.

**[00154]** The present invention further encompasses formulations comprising antibodies that are conjugated to a therapeutic moiety. An antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic

agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Therapeutic moieties include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), Auristatin molecules (e.g., auristatin PHE, bryostatin 1, and solastatin 10; see Woyke et al., *Antimicrob. Agents Chemother.* 46:3802-8 (2002), Woyke et al., *Antimicrob. Agents Chemother.* 45:3580-4 (2001), Mohammad *et al.*, *Anticancer Drugs* 12:735-40 (2001), Wall et al., *Biochem. Biophys. Res. Commun.* 266:76-80 (1999), Mohammad et al., *Int. J. Oncol.* 15:367-72 (1999), all of which are incorporated herein by reference), hormones (e.g., glucocorticoids, progestins, androgens, and estrogens), DNA-repair enzyme inhibitors (e.g., etoposide or topotecan), kinase inhibitors (e.g., compound ST1571, imatinib mesylate (Kantaijian et al., *Clin Cancer Res.* 8(7):2167-76 (2002)), cytotoxic agents (e.g., paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof) and those compounds disclosed in U.S. Pat. Nos. 6,245,759, 6,399,633, 6,383,790, 6,335,156, 6,271,242, 6,242,196, 6,218,410, 6,218,372, 6,057,300, 6,034,053, 5,985,877, 5,958,769, 5,925,376, 5,922,844, 5,911,995, 5,872,223, 5,863,904, 5,840,745, 5,728,868, 5,648,239, 5,587,459), farnesyl transferase inhibitors (e.g., R115777, BMS-214662, and those disclosed by, for example, U.S. Pat. Nos. 6,458,935, 6,451,812, 6,440,974, 6,436,960, 6,432,959, 6,420,387, 6,414,145, 6,410,541, 6,410,539, 6,403,581, 6,399,615, 6,387,905, 6,372,747, 6,369,034, 6,362,188, 6,342,765, 6,342,487, 6,300,501, 6,268,363, 6,265,422, 6,248,756, 6,239,140, 6,232,338, 6,228,865, 6,228,856, 6,225,322, 6,218,406, 6,211,193, 6,187,786, 6,169,096, 6,159,984, 6,143,766, 6,133,303, 6,127,366, 6,124,465, 6,124,295, 6,103,723, 6,093,737, 6,090,948, 6,080,870, 6,077,853, 6,071,935, 6,066,738, 6,063,930, 6,054,466, 6,051,582, 6,051,574, and 6,040,305), topoisomerase inhibitors (e.g., camptothecin; irinotecan; SN-38; topotecan; 9-aminocamptothecin; GG-211 (GI 147211); DX-895 If; IST-622; rubitecan; pyrazoloacridine; XR-5000; saintopin; UCE6; UCE1022; TAN-1518A; TAN-1518B; KT6006; KT6528; ED-110; NB-506; ED-110; NB-506; and rebeccamycin); bulgarein; DNA minor groove binders such as Hoescht dye 33342 and Hoechst dye 33258; nitidine; fagaronine; epiberberine; coralyne; beta-

lapachone; BC-4-1; bisphosphonates (e.g., alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate) HMG-CoA reductase inhibitors, (e.g., lovastatin, simvastatin, atorvastatin, pravastatin, fluvastatin, statin, cerivastatin, lescol, lupitor, rosuvastatin and atorvastatin) and pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof. See, e.g., Rothenberg, M. L., *Annals of Oncology* 8:837-855(1997); and Moreau, P., et al., *J. Med. Chem.* 41:1631-1640(1998)), antisense oligonucleotides (e.g., those disclosed in the U.S. Pat. Nos. 6,277,832, 5,998,596, 5,885,834, 5,734,033, and 5,618,709), immunomodulators (e.g., antibodies and cytokines), antibodies, and adenosine deaminase inhibitors (e.g., Fludarabine phosphate and 2-Chlorodeoxyadenosine).

**[00155]** Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF $\alpha$ , TNF $\beta$ , AIM I (see, International publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., 1994, *J. Immunol.*, 6:1567-1574), and VEGI (see, International publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin, endostatin or a component of the coagulation pathway (e.g., tissue factor); or, a biological response modifier such as, for example, a lymphokine (e.g., interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), a growth factor (e.g., growth hormone ("GH")), or a coagulation agent (e.g., calcium, vitamin K, tissue factors, such as but not limited to, Hageman factor (factor XII), high-molecular-weight kininogen (HMWK), prekallikrein (PK), coagulation proteins-factors II (prothrombin), factor V, XIIa, VIII, XIIIa, XI, XIa, IX, IXa, X, phospholipid, fibrinopeptides A and B from the  $\alpha$  and  $\beta$  chains of fibrinogen, fibrin monomer).

**[00156]** Moreover, an antibody can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alpha-emitters such as  $^{213}\text{Bi}$  or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to,  $^{131}\text{In}$ ,  $^{131}\text{Lu}$ ,  $^{131}\text{Y}$ ,  $^{131}\text{Ho}$ ,  $^{131}\text{Sm}$ , to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-

tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res. 4(10):2483-90; Peterson et al., 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman et al., 1999, Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

**[00157]** Techniques for conjugating therapeutic moieties to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, Immunol. Rev. 62:119-58.

**[00158]** Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Pat. No. 4,676,980, which is incorporated herein by reference in its entirety.

**[00159]** The therapeutic moiety or drug conjugated to an antibody or fragment thereof should be chosen to achieve the desired prophylactic or therapeutic effect(s) for a particular disorder in a subject. A clinician or other medical personnel should consider the following when deciding on which therapeutic moiety or drug to conjugate to an antibody or fragment thereof: the nature of the disease, the severity of the disease, and the condition of the subject.

**[00160]** Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

### **5.3.2 Formulations Comprising Purified Antibodies that Specifically Bind to a Particular Antigen**

**[00161]** In further embodiments, the present invention encompasses formulations comprising isolated antibodies or compositions comprising antibodies, wherein said antibodies specifically bind to one or more particular antigens. In certain embodiments, the antibody of the



present invention specifically binds to an antigen of respiratory syncytial virus (RSV). In other embodiments, the antibody of the present invention specifically binds to an antigen of human metapneumovirus (hMPV). In some embodiments, the antibody is a humanized antibody that specifically binds to an antigen of hMPV. In certain embodiments, the antibody of the present invention specifically binds to integrin  $\alpha_v\beta_3$ . In some embodiments, the antibody is MEDI-522 (Vitaxin®). In certain embodiments, the antibody of the present invention specifically binds to CD2. In some embodiments, the antibody is siplizumab. In certain embodiments, the antibody of the present invention specifically binds to CD19. In some embodiments, the antibody is MT-103. In further embodiments, the antibody of the present invention specifically binds to EphA2. In some embodiments, the antibody is human or humanized EA2 or EA5. In certain embodiments, the antibody of the present invention specifically binds to EphA4. In some embodiments, the antibody is a humanized antibody that specifically binds to EphA4. In certain embodiments, the antibody of the present invention specifically binds to IL-9. In some embodiments, the antibody is a human or humanized antibody that specifically binds to IL-9. In some embodiments, the antibody is MEDI-528.

**[00162]** In some embodiments, the antibody is not palivizumab. In some embodiments, the antibody is not MEDI-522 (Vitaxin®). In some embodiments, the antibody is not siplizumab. In some embodiments, the antibody is not MT-103. In some embodiments, the antibody is not human or humanized EA2 or EA5. In some embodiments, the antibody is not MEDI-528.

**[00163]** The antibodies useful in the present invention may be high potency antibodies. High potency antibodies can be produced by genetically engineering appropriate antibody gene sequences and expressing the antibody sequences in a suitable host. The antibodies produced can be screened to identify antibodies with, *e.g.*, high  $k_{on}$  values in a BIAcore assay.

**[00164]** In certain embodiments, the antibodies useful in the present invention have a high binding affinity for one or more antigens. In a specific embodiment, the antibodies of the present invention have an association rate constant or  $k_{on}$  rate (antibody (Ab) + antigen (Ag) <sup>$k_{on}$</sup>   $\rightarrow$  Ab-Ag) of at least  $10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^7 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ , or at least  $10^8 \text{ M}^{-1}\text{s}^{-1}$ . In a preferred embodiment, the antibodies of the present invention have a  $k_{on}$  of at least  $2 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ , at least  $10^7 \text{ M}^{-1}\text{s}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ , or at least  $10^8 \text{ M}^{-1}\text{s}^{-1}$ .

**[00165]** In another embodiment, the antibodies of the present invention have a  $k_{\text{off}}$  rate (antibody (Ab) + antigen) of less than  $10^{-1} \text{ s}^{-1}$ , less than  $5 \times 10^{-1} \text{ s}^{-1}$ , less than  $10^{-2} \text{ s}^{-1}$ , less than  $5 \times 10^{-2} \text{ s}^{-1}$ , less than  $10^{-3} \text{ s}^{-1}$ , less than  $5 \times 10^{-3} \text{ s}^{-1}$ , less than  $10^{-4} \text{ s}^{-1}$ , less than  $5 \times 10^{-4} \text{ s}^{-1}$ , less than  $10^{-5} \text{ s}^{-1}$ , less than  $5 \times 10^{-5} \text{ s}^{-1}$ , less than  $10^{-6} \text{ s}^{-1}$ , less than  $5 \times 10^{-6} \text{ s}^{-1}$ , less than  $10^{-7} \text{ s}^{-1}$ , less than  $5 \times 10^{-7} \text{ s}^{-1}$ , less than  $10^{-8} \text{ s}^{-1}$ , less than  $5 \times 10^{-8} \text{ s}^{-1}$ , less than  $10^{-9} \text{ s}^{-1}$ , less than  $5 \times 10^{-9} \text{ s}^{-1}$ , or less than  $10^{-10} \text{ s}^{-1}$ . In a preferred embodiment, the antibodies of the present invention have a  $k_{\text{on}}$  of less than  $5 \times 10^{-4} \text{ s}^{-1}$ , less than  $10^{-5} \text{ s}^{-1}$ , less than  $5 \times 10^{-5} \text{ s}^{-1}$ , less than  $10^{-6} \text{ s}^{-1}$ , less than  $5 \times 10^{-6} \text{ s}^{-1}$ , less than  $10^{-7} \text{ s}^{-1}$ , less than  $5 \times 10^{-7} \text{ s}^{-1}$ , less than  $10^{-8} \text{ s}^{-1}$ , less than  $5 \times 10^{-8} \text{ s}^{-1}$ , less than  $10^{-9} \text{ s}^{-1}$ , less than  $5 \times 10^{-9} \text{ s}^{-1}$ , or less than  $10^{-10} \text{ s}^{-1}$ .

**[00166]** In certain embodiments, the antibodies of the present invention have an affinity constant or  $K_a$  ( $k_{\text{on}}/k_{\text{off}}$ ) of at least  $10^2 \text{ M}^{-1}$ , at least  $5 \times 10^2 \text{ M}^{-1}$ , at least  $10^3 \text{ M}^{-1}$ , at least  $5 \times 10^3 \text{ M}^{-1}$ , at least  $10^4 \text{ M}^{-1}$ , at least  $5 \times 10^4 \text{ M}^{-1}$ , at least  $10^5 \text{ M}^{-1}$ , at least  $5 \times 10^5 \text{ M}^{-1}$ , at least  $10^6 \text{ M}^{-1}$ , at least  $5 \times 10^6 \text{ M}^{-1}$ , at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , at least  $10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ . The present invention also provides formulations comprising one or more antibodies which immunospecifically bind to an antigen with an affinity constant of at least  $2 \times 10^8 \text{ M}^{-1}$ , at least  $2.5 \times 10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , at least  $5 \times 10^{12} \text{ M}^{-1}$ , at least  $10^{13} \text{ M}^{-1}$ , at least  $5 \times 10^{13} \text{ M}^{-1}$ , at least  $10^{14} \text{ M}^{-1}$ , at least  $5 \times 10^{14} \text{ M}^{-1}$ , at least  $10^{15} \text{ M}^{-1}$ , or at least  $5 \times 10^{15} \text{ M}^{-1}$ .

**[00167]** In yet another embodiment, the antibodies useful in the present invention have a dissociation constant or  $K_d$  ( $k_{\text{off}}/k_{\text{on}}$ ) of less than  $10^{-2} \text{ M}$ , less than  $5 \times 10^{-2} \text{ M}$ , less than  $10^{-3} \text{ M}$ , less than  $5 \times 10^{-3} \text{ M}$ , less than  $10^{-4} \text{ M}$ , less than  $5 \times 10^{-4} \text{ M}$ , less than  $10^{-5} \text{ M}$ , less than  $5 \times 10^{-5} \text{ M}$ , less than  $10^{-6} \text{ M}$ , less than  $5 \times 10^{-6} \text{ M}$ , less than  $10^{-7} \text{ M}$ , less than  $5 \times 10^{-7} \text{ M}$ , less than  $10^{-8} \text{ M}$ , less than  $5 \times 10^{-8} \text{ M}$ , less than  $10^{-9} \text{ M}$ , less than  $5 \times 10^{-9} \text{ M}$ , less than  $10^{-10} \text{ M}$ , less than  $5 \times 10^{-10} \text{ M}$ , less than  $10^{-11} \text{ M}$ , less than  $5 \times 10^{-11} \text{ M}$ , less than  $10^{-12} \text{ M}$ , less than  $5 \times 10^{-12} \text{ M}$ , less than  $10^{-13} \text{ M}$ , less than  $5 \times 10^{-13} \text{ M}$ , less than  $10^{-14} \text{ M}$ , less than  $5 \times 10^{-14} \text{ M}$ , less than  $10^{-15} \text{ M}$ , or less than  $5 \times 10^{-15} \text{ M}$ .

**[00168]** In certain embodiments, the antibodies useful in the present invention have a median effective concentration ( $\text{EC}_{50}$ ) of less than  $0.01 \text{ nM}$ , less than  $0.025 \text{ nM}$ , less than  $0.05 \text{ nM}$ , less than  $0.1 \text{ nM}$ , less than  $0.25 \text{ nM}$ , less than  $0.5 \text{ nM}$ , less than  $0.75 \text{ nM}$ , less than  $1 \text{ nM}$ ,

less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay. The median effective concentration is the concentration of antibody or antibody fragments that neutralizes 50% of an antigen in an *in vitro* microneutralization assay. In a preferred embodiment, the antibodies of the present invention have an EC<sub>50</sub> of less than 0.01 nM, less than 0.025 nM, less than 0.05 nM, less than 0.1 nM, less than 0.25 nM, less than 0.5 nM, less than 0.75 nM, less than 1 nM, less than 1.25 nM, less than 1.5 nM, less than 1.75 nM, or less than 2 nM, in an *in vitro* microneutralization assay.

**[00169]** The present invention also provides antibodies that immunospecifically bind to an antigen of interest, the antibodies comprising derivatives of the VH domains, VH CDRs, VL domains, and VL CDRs described herein that immunospecifically bind to antigens of interest. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In a preferred embodiment, the derivatives have conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

### **5.3.3 Antibodies that Immunospecifically Bind to RSV antigen**

**[00170]** It should be recognized that antibodies that immunospecifically bind to a RSV antigen are known in the art. For example, palivizumab is a humanized monoclonal antibody

presently used for the prevention of RSV infection in pediatric patients. The present invention provides formulations of antibodies that immunospecifically bind to one or more RSV antigens. Preferably, the antibodies useful in the invention immunospecifically bind to one or more RSV antigens regardless of the strain of RSV. The present invention also provides antibodies that differentially or preferentially bind to RSV antigens from one strain of RSV versus another RSV strain. In a specific embodiment, the formulations comprise antibodies that immunospecifically bind to the RSV F glycoprotein, G glycoprotein or SH protein. In a preferred embodiment, the formulations comprise antibodies that immunospecifically bind to the RSV F glycoprotein. In another preferred embodiment, the formulations comprise antibodies that bind to the A, B, or C antigenic sites of the RSV F glycoprotein.

**[00171]** The formulations of the invention comprise antibodies that immunospecifically bind to a RSV antigen and have a dissociation constant ( $K_D$ ) of less than 3000 pM, less than 2500 pM, less than 2000 pM, less than 1500 pM, less than 1000 pM, less than 750 pM, less than 500 pM, less than 250 pM, less than 200 pM, less than 150 pM, less than 100 pM, less than 75 pM as assessed using an described herein or known to one of skill in the art (*e.g.*, a BIAcore assay). In a specific embodiment, formulations of the invention comprise antibodies that immunospecifically bind to a RSV antigen and have a dissociation constant ( $K_D$ ) of between 25 to 3400 pM, 25 to 3000 pM, 25 to 2500 pM, 25 to 2000 pM, 25 to 1500 pM, 25 to 1000 pM, 25 to 750 pM, 25 to 500 pM, 25 to 250 pM, 25 to 100 pM, 25 to 75 pM, 25 to 50 pM as assessed using an described herein or known to one of skill in the art (*e.g.*, a BIAcore assay). In another embodiment, formulations of the invention comprise antibodies that immunospecifically bind to a RSV antigen and have a dissociation constant ( $K_D$ ) of 500 pM, preferably 100 pM, more preferably 75 pM and most preferably 50 pM as assessed using an described herein or known to one of skill in the art (*e.g.*, a BIAcore assay).

**[00172]** The present invention provides formulations that comprise antibodies that have a median inhibitory concentration ( $IC_{50}$ ) of less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, less than 1.75 nM, less than 1.5 nM, less than 1.25 nM, less than 1 nM, less than 0.75 nM, less than 0.5 nM, less than 0.25 nM, less than 0.1 nM, less than 0.05 nM, less than 0.025 nM, or less than 0.01 nM, in an *in vitro* microneutralization assay. The  $IC_{50}$  is the concentration of antibody that neutralizes 50% of the RSV in an *in vitro* microneutralization assay. In a preferred embodiment, antibody of the invention has an  $IC_{50}$  of less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, less than 1.75 nM, less than 1.5 nM, less than 1.25 nM, less than

1 nM, less than 0.75 nM, less than 0.5 nM, less than 0.25 nM, less than 0.1 nM, less than 0.05 nM, less than 0.025 nM, or less than 0.01 nM, in an *in vitro* microneutralization assay.

**[00173]** In a specific embodiment, the formulations of the invention comprise an antibody that has approximately 20-fold, 25-fold, 30-fold, 35-fold, 40-fold, 45-fold, 50-fold, 55-fold, 60-fold, 65-fold, 70-fold, 75-fold, 80-fold, 90-fold, 100-fold or higher affinity for a RSV F antigen than palivizumab or an antibody-binding fragment thereof as assessed by an assay known in the art or described herein (*e.g.*, a BIAcore assay). In another embodiment, formulations of the invention comprise antibodies that have an approximately 1-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, or more higher  $K_a$  than palivizumab or an antigen-binding fragment thereof as assessed by an assay known in the art or described herein. In another embodiment, a formulation of the invention comprises an antibody that is approximately 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, or 20-fold or more potent than palivizumab or an antigen-binding fragment thereof in an *in vitro* microneutralization assay such as described herein. The amino acid sequence of palivizumab is disclosed, *e.g.*, in Johnson et al., 1997, J. Infectious Disease 176:1215-1224, and U.S. Patent No. 5,824,307, each of which is incorporated herein by reference in its entirety. In a specific embodiment, a formulation of the invention comprise an antibody that is not palivizumab or a fragment of palivizumab or an antigen-binding fragment of palivizumab, *e.g.*, is not an antibody comprising a VH domain of SEQ ID NO:7 and/or a VL domain of SEQ ID NO:8.

**[00174]** The present invention provides antibodies that immunospecifically bind to one or more RSV antigens, said antibodies comprising the amino acid sequence of palivizumab with one or more amino acid residue substitutions in the variable light (VL) domain and/or variable heavy (VH) domain depicted in FIG. 3. The present invention also provides antibodies that immunospecifically bind to one or more RSV antigens, said antibodies comprising the amino acid sequence of palivizumab with one or more amino acid residue substitutions in one or more VL CDRs and/or one or more VH CDRs. In a specific embodiment, an antibody comprises the amino acid sequence of palivizumab with one or more amino acid residue substitutions of the amino acid residues indicated in bold face and underlining in Table 1. In another embodiment, an antibody comprises the amino sequence of palivizumab with one or more amino acid residue substitutions of the amino acid residues indicated in bold face and underlining in Table 1 and one or more amino acid residue substitutions of the framework regions of the variable domains of palivizumab (*e.g.*, mutations in framework region 4 of the heavy and/or light variable

domains). In accordance with these embodiments, the amino acid residue substitutions can be conservative or non-conservative. The antibody generated by introducing substitutions in the VH domain, VH CDRs, VL domain and/or VL CDRs of palivizumab can be tested *in vitro* and *in vivo*, for example, for its ability to bind to RSV F antigen, for its ability to neutralize RSV, or for its ability to prevent, treat or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof).

**Table 1. CDR Sequences of palivizumab**

CDR	Sequence	SEQ ID NO:
VH1	T <u>S</u> GMSVG	1
VH2	DIWWDD <u>K</u> <u>K</u> DYNPSL <u>K</u> <u>S</u>	2
VH3	<u>S</u> MITN <u>W</u> YFDV	3
VL1	<u>K</u> <u>C</u> <u>Q</u> <u>L</u> <u>S</u> VG <sup>Y</sup> MH	4
VL2	DT <u>S</u> <u>K</u> <u>L</u> <u>A</u> <u>S</u>	5
VL3	FQGS <u>G</u> Y <u>P</u> <u>F</u> <u>T</u>	6

\* Bold faced & underlined amino acid residues are preferred residues which should be substituted.

[00175] The formulations of the present invention also comprise those antibodies and antigen-binding fragments of the antibodies referenced in Table 2 and the Examples Section of the application. In a specific embodiment, a formulation of the present invention comprises antibody AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4. In another embodiment, a formulation of the present invention comprises an antigen-binding fragment (*e.g.*, a Fab fragment of) AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4. In a preferred embodiment, a formulation of the present invention comprises antibody A4B4L1FR-S28R or an antigen-binding fragment thereof.

**[00176]** In some embodiments, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and/or A17h4 comprise the framework region and constant regions of palivizumab (see FIG. 3). In preferred embodiments, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and/or A17h4 comprise the framework region and constant regions of palivizumab with the exception that there is an amino acid substitution of an A105Q in the heavy chain framework 4 (FR4) (numbering used herein according to Kabat et al. (1991). Sequences of proteins of immunological interest. (U.S. Department of Health and Human Services, Washington, D.C.) 5<sup>th</sup> ed.) ("Kabat numbering") (*i.e.*, position 112 in SEQ ID NO:7 (palivizumab VH domain)) and an L104V in the light chain FR4 (*i.e.*, position 103 in SEQ ID NO:8 (palivizumab VL domain)). An example of antibodies comprising a framework with these VH and VL single mutations is shown in FIG. 4 (1X-493L1FR) and in FIG. 5 (A4B4L1FR-S28R).

**[00177]** In a specific embodiment, the present invention provides one or more antibodies that immunospecifically bind to one or more RSV F antigens, said antibodies comprising a VH chain and/or VL chain having the amino acid sequence of a VH chain and/or VL chain of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4. In a preferred embodiment, an antibody of the invention immunospecifically binds to a RSV F antigen, and said antibody comprises a VH chain and/or a VL chain having the amino acid sequence of the VH and/or VL chain of A4B4L1FR-S28 (VH chain, SEQ ID NO:254; VL chain SEQ ID NO:255). In another embodiment, the present invention provides one or more antibodies that immunospecifically bind to one or more RSV antigens, said antibodies comprising a VH domain and/or VL domain having the amino acid sequence of a VH domain and/or VL domain of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R, A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4. In a preferred embodiment, an antibody of the invention immunospecifically binds to a RSV F antigen, and said antibody comprises a VH domain and/or VL domain having the amino acid sequence of the

VH domain and/or VL domain of A4B4L1FR-S28R (VH domain, SEQ ID NO:48; VL domain, SEQ ID NO:11).

**[00178]** In another embodiment, the present invention provides antibodies that immunospecifically bind to one or more RSV antigens, said antibodies comprising one, two, three, or more CDRs having the amino acid sequence of one, two, three, or more CDRs of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (MEDI-524, motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4. In a preferred embodiment, a formulation of the present invention comprises an antibody that immunospecifically binds to a RSV antigen, and said antibody comprises one, two, three, or more CDRs having the amino acid sequence of one, two, three, or more CDRs of A4B4L1FR-S28R. In yet another embodiment, the formulation of the present invention comprises an antibody that immunospecifically binds to one or more RSV F antigens, said antibodies comprising a combination of VH CDRs and/or VL CDRs having the amino acid sequence of VH CDRs and/or VL CDRs of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and/or A17h4. In a preferred embodiment, a formulation of the present invention comprises an antibody that immunospecifically binds to a RSV F antigen and said antibody comprises a combination of VH CDRs and/or VL CDRs having the amino acid sequence of the VH CDRs and/or VL CDRs of A4B4L1FR-S28R.

**[00179]** The present invention provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigen), said antibodies comprising a variable heavy ("VH") chain having an amino acid sequence of any one of the VH chains listed in Table 2. In certain embodiments, the antibody is not palivizumab and/or the VH chain is not the VH chain of palivizumab.

**[00180]** The invention also provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigen), said antibodies comprising a VH domain having an amino acid sequence of any one of the VH domains listed in Table 2. In certain embodiments of the invention, the antibody is not palivizumab and/or the VH domain is not the VH domain of palivizumab.



**[00181]** The present invention also provides antibodies that immunospecifically bind to one or more RSV antigens, said antibodies comprising a VH complementarity determining region ("CDR") (*e.g.*, VH CDR1, VH CDR2, and/or VH CDR3) having an amino acid sequence of any of the VH CDRs listed in Table 2 and/or Tables 3A-3C. In certain embodiments of the invention, an antibody comprising a VH CDR having an amino acid of any of one of the VH CDRs listed in Table 2 and/or Tables 3A-3C is not palivizumab. In some embodiments, the antibody or binding fragment thereof comprises one, two or three of the VH CDRs listed in Table 2 and/or Tables 3A-3C.

Table 2. Antibodies &amp; Fragments Thereof

Antibody Name	VH Chain	VH Domain	VH CDR1	VH CDR2	VH CDR3	VL Chain	VL Domain	VL CDR1	VL CDR2	VL CDR3
**palivizumab	SEQ ID NO:208	SEQ ID NO:7	TSGMSVG (SEQ ID NO:1)	DIWDDKKDYN PSLKS (SEQ ID NO:2)	SMITNWFYFDV (SEQ ID NO:3)	SEQ ID NO:209	SEQ ID NO:8	KCQLSVGYMH (SEQ ID NO:4)	DTSKLAS (SEQ ID NO:5)	FOGSGYPFT (SEQ ID NO:6)
***A12f2	SEQ ID NO:210	SEQ ID NO:9	TAGMSVG (SEQ ID NO:10)	DIWDDKKDYN PSLKS (SEQ ID NO:2)	SMITNWFYFDV (SEQ ID NO:12)	SEQ ID NO:211	SEQ ID NO:13	SASSSVGYMH (SEQ ID NO:14)	DTEKLAS (SEQ ID NO:15)	FOGSGYPFT (SEQ ID NO:16)
***P12f2	SEQ ID NO:212	SEQ ID NO:17	TPGMSVG (SEQ ID NO:18)	DIWDDKKHYN PSLKD (SEQ ID NO:19)	DMITNWFYFDV (SEQ ID NO:20)	SEQ ID NO:213	SEQ ID NO:21	SLSSRVGYMH (SEQ ID NO:22)	DTEKLSS (SEQ ID NO:23)	FOGSGYPFT (SEQ ID NO:24)
***P12f4	SEQ ID NO:214	SEQ ID NO:24	TPGMSVG (SEQ ID NO:18)	DIWDDKKHYN PSLKD (SEQ ID NO:25)	DMITNWFYFDV (SEQ ID NO:29)	SEQ ID NO:215	SEQ ID NO:26	SLSSRVGYMH (SEQ ID NO:22)	DTRGIPS (SEQ ID NO:27)	FOGSGYPFT (SEQ ID NO:28)
***P11d4	SEQ ID NO:216	SEQ ID NO:28	TPGMSVG (SEQ ID NO:18)	DIWDDKKHYN PSLKD (SEQ ID NO:25)	DMITNWFYFDV (SEQ ID NO:29)	SEQ ID NO:217	SEQ ID NO:30	SPSSRVGYMH (SEQ ID NO:31)	DTMRLAS (SEQ ID NO:32)	FOGSGYPFT (SEQ ID NO:33)
***A1e9	SEQ ID NO:218	SEQ ID NO:33	TAGMSVG (SEQ ID NO:10)	DIWDDKKHYN PSLKD (SEQ ID NO:25)	DMITNWFYFDV (SEQ ID NO:29)	SEQ ID NO:219	SEQ ID NO:34	SLSSRVGYMH (SEQ ID NO:22)	DTEKLSS (SEQ ID NO:35)	FOGSGYPFT (SEQ ID NO:36)
***A12a6	SEQ ID NO:220	SEQ ID NO:36	TAGMSVG (SEQ ID NO:10)	DIWDDKKDYN PSLKD (SEQ ID NO:37)	DMITNWFYFDV (SEQ ID NO:20)	SEQ ID NO:221	SEQ ID NO:38	SASSRVGYMH (SEQ ID NO:39)	DTEKLSS (SEQ ID NO:40)	FOGSGYPFT (SEQ ID NO:41)
***A13c4	SEQ ID NO:222	SEQ ID NO:40	TAGMSVG (SEQ ID NO:10)	DIWDDKKSYN PSLKD (SEQ ID NO:41)	DMITNWFYFDV (SEQ ID NO:20)	SEQ ID NO:223	SEQ ID NO:42	SLSSRVGYMH (SEQ ID NO:22)	DTMQSS (SEQ ID NO:43)	FOGSGYPFT (SEQ ID NO:44)
***A17d4	SEQ ID NO:224	SEQ ID NO:44	TAGMSVG (SEQ ID NO:10)	DIWDDKKSYN PSLKD (SEQ ID NO:45)	DMITNWFYFDV (SEQ ID NO:20)	SEQ ID NO:225	SEQ ID NO:46	LPSSRVGYMH (SEQ ID NO:47)	DTMQSS (SEQ ID NO:48)	FOGSGYPFT (SEQ ID NO:49)
***A4B4	SEQ ID NO:226	SEQ ID NO:48	TAGMSVG (SEQ ID NO:10)	DIWDDKKHYN PSLKD (SEQ ID NO:19)	DMITNWFYFDV (SEQ ID NO:20)	SEQ ID NO:227	SEQ ID NO:49	SASSRVGYMH (SEQ ID NO:39)	DTFTLDS (SEQ ID NO:50)	FOGSGYPFT (SEQ ID NO:51)
***A8c7	SEQ ID NO:228	SEQ ID NO:51	TAGMSVG (SEQ ID NO:10)	DIWDDKKSYN PSLKD (SEQ ID NO:45)	DMITNWFYFDV (SEQ ID NO:29)	SEQ ID NO:229	SEQ ID NO:52	SPSSRVGYMH (SEQ ID NO:31)	DTRYQSS (SEQ ID NO:53)	FOGSGYPFT (SEQ ID NO:54)
*IX-493L1FR	SEQ ID NO:230	SEQ ID NO:343	TSGMSVG (SEQ ID NO:1)	DIWDDKKDYN PSLKS (SEQ ID NO:2)	SMITNWFYFDV (SEQ ID NO:3)	SEQ ID NO:231	SEQ ID NO:54	SASSSVGYMH (SEQ ID NO:14)	DTSKLAS (SEQ ID NO:5)	FOGSGYPFT (SEQ ID NO:6)

*H3-3F4	SEQ ID NO: 232	SEQ ID NO: 55	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 29)	SEQ ID NO: 233	SEQ ID NO: 56	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*M3H9	SEQ ID NO: 234	SEQ ID NO: 55	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 29)	SEQ ID NO: 235	SEQ ID NO: 70	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*Y10H6	SEQ ID NO: 236	SEQ ID NO: 55	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 29)	SEQ ID NO: 237	SEQ ID NO: 58	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*DG (aka D95/G93)	SEQ ID NO: 238	SEQ ID NO: 78	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 29)	SEQ ID NO: 239	SEQ ID NO: 56	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
AFF(1)	SEQ ID NO: 240	SEQ ID NO: 9	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 12)	SEQ ID NO: 241	SEQ ID NO: 60	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*6H8	SEQ ID NO: 242	SEQ ID NO: 78	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 79)	SEQ ID NO: 243	SEQ ID NO: 62	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*L1-7E5	SEQ ID NO: 244	SEQ ID NO: 78	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 79)	SEQ ID NO: 245	SEQ ID NO: 64	SASSSVGYMH (SEQ ID NO: 39)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*L2-15B10	SEQ ID NO: 246	SEQ ID NO: 78	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 2)	DMITNWFYDV (SEQ ID NO: 79)	SEQ ID NO: 247	SEQ ID NO: 65	SASSSVGYMH (SEQ ID NO: 14)	DTFKLAS (SEQ ID NO: 15)	FQSGYPFT (SEQ ID NO: 6)
*A13a11	SEQ ID NO: 248	SEQ ID NO: 67	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 19)	DMITNWFYDV (SEQ ID NO: 29)	SEQ ID NO: 249	SEQ ID NO: 68	SPSSRVGYMH (SEQ ID NO: 31)	DTYRHS (SEQ ID NO: 69)	FQSGYPFT (SEQ ID NO: 6)
*A1h5	SEQ ID NO: 250	SEQ ID NO: 33	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 25)	DMITNWFYDV (SEQ ID NO: 29)	SEQ ID NO: 251	SEQ ID NO: 71	SLSSSVGYMH (SEQ ID NO: 72)	DTYRHS (SEQ ID NO: 73)	FQSGYPFT (SEQ ID NO: 6)
A4B4 (1)	SEQ ID NO: 252	SEQ ID NO: 48	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 19)	DMITNWFYDV (SEQ ID NO: 20)	SEQ ID NO: 253	SEQ ID NO: 74	SASSRVGYMH (SEQ ID NO: 39)	DTYRHS (SEQ ID NO: 75)	FQSGYPFT (SEQ ID NO: 6)
***A4B4L1F R-S28R (aka motavizumab)	SEQ ID NO: 254	SEQ ID NO: 48	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 19)	DMITNWFYDV (SEQ ID NO: 20)	SEQ ID NO: 255	SEQ ID NO: 11	SASSRVGYMH (SEQ ID NO: 39)	DTYRHS (SEQ ID NO: 5)	FQSGYPFT (SEQ ID NO: 6)
***A4B4-F52S	SEQ ID NO: 256	SEQ ID NO: 48	TAGMSVG (SEQ ID NO: 10)	DIWDDKKDYN PSLKS (SEQ ID NO: 19)	DMITNWFYDV (SEQ ID NO: 20)	SEQ ID NO: 257	SEQ ID NO: 76	SASSRVGYMH (SEQ ID NO: 39)	DTYRHS (SEQ ID NO: 77)	FQSGYPFT (SEQ ID NO: 6)

***A17d4 (1)	SEQ ID NO:222	SEQ ID NO:40	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:41)	DMIFENWYFDV (SEQ ID NO:20)	SEQ ID NO:225	SEQ ID NO:46	LPSSRVGYMH (SEQ ID NO:47)	D <del>MY</del> QSS (SEQ ID NO:43)	FQSGGYPFT (SEQ ID NO:6)
***A3e2	SEQ ID NO:303	SEQ ID NO:304	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:305)	DMIFENWYFDV (SEQ ID NO:29)	SEQ ID NO:306	SEQ ID NO:307	SASSSVGYMH (SEQ ID NO:14)	DIFYLHS (SEQ ID NO:308)	FQSGGYPFT (SEQ ID NO:6)
***A14a4	SEQ ID NO:309	SEQ ID NO:310	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:45)	DMITNWIYFDV (SEQ ID NO:311)	SEQ ID NO:312	SEQ ID NO:313	LLSSRVGYMH (SEQ ID NO:314)	D <del>TY</del> QTS (SEQ ID NO:315)	FQSGGYPFT (SEQ ID NO:6)
***A16b4	SEQ ID NO:316	SEQ ID NO:317	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:19)	DMIFENWYFDV (SEQ ID NO:29)	SEQ ID NO:318	SEQ ID NO:319	LLSSRVGYMH (SEQ ID NO:320)	D <del>MY</del> QAS (SEQ ID NO:321)	FQSGGYPFT (SEQ ID NO:6)
***A17b5	SEQ ID NO:322	SEQ ID NO:323	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:19)	DMIFENWYFDV (SEQ ID NO:29)	SEQ ID NO:324	SEQ ID NO:325	SLSSRVGYMH (SEQ ID NO:22)	D <del>TY</del> ILPS (SEQ ID NO:326)	FQSGGYPFT (SEQ ID NO:6)
***A17f5	SEQ ID NO:327	SEQ ID NO:328	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:329)	DMIFENWYFDV (SEQ ID NO:29)	SEQ ID NO:330	SEQ ID NO:331	SLSSRVGYMH (SEQ ID NO:22)	D <del>TF</del> RHTS (SEQ ID NO:332)	FQSGGYPFT (SEQ ID NO:6)
***A17h4	SEQ ID NO:218	SEQ ID NO:33	TAGMSVG (SEQ ID NO:10)	DIWWDGKKSYN PSLKD (SEQ ID NO:25)	DMIFENWYFDV (SEQ ID NO:29)	SEQ ID NO:333	SEQ ID NO:334	SPSSSVGYMH (SEQ ID NO:335)	D <del>TY</del> ILAS (SEQ ID NO:336)	FQSGGYPFT (SEQ ID NO:6)

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in palivizumab; Fab fragment produced (\*); Monoclonal antibody produced (\*\*); Fab fragment & monoclonal antibody produced (\*\*\*)

**Table 3A - VH CDR1 Sequences**

SVG (SEQ ID NO:1)
SVG (SEQ ID NO:10)
SVG (SEQ ID NO:18)

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in palivizumab

**Table 3B - VH CDR2 Sequences**

DDKKDYNPSLKS (SEQ ID NO:2)	<b>D</b> <b>G</b> <b>K</b> <b>K</b> DYNPSLKS (SEQ ID NO:100)
DDKKDYNPSL <b>KD</b> (SEQ ID NO:86)	<b>D</b> <b>G</b> <b>K</b> <b>K</b> DYNPSL <b>KD</b> (SEQ ID NO:103)
DDK <b>KH</b> YNPSLKS (SEQ ID NO:82)	<b>D</b> <b>G</b> <b>K</b> <b>KH</b> YNPSLKS (SEQ ID NO:106)
DDK <b>KH</b> YNPSL <b>KD</b> (SEQ ID NO:19)	<b>D</b> <b>G</b> <b>K</b> <b>KH</b> YNPSL <b>KD</b> (SEQ ID NO:25)
DDK <b>KS</b> YNPSLKS (SEQ ID NO:109)	<b>D</b> <b>G</b> <b>K</b> <b>KS</b> YNPSLKS (SEQ ID NO:114)
DDK <b>KS</b> YNPSL <b>KD</b> (SEQ ID NO:111)	<b>D</b> <b>G</b> <b>K</b> <b>KS</b> YNPSL <b>KD</b> (SEQ ID NO:41)
DDK <b>G</b> DYNPSLKS (SEQ ID NO:384)	<b>D</b> <b>G</b> <b>K</b> <b>G</b> DYNPSLKS (SEQ ID NO:390)
DDK <b>G</b> DYNPSL <b>KD</b> (SEQ ID NO:385)	<b>D</b> <b>G</b> <b>K</b> <b>G</b> DYNPSL <b>KD</b> (SEQ ID NO:391)
DDK <b>G</b> HYNPSLKS (SEQ ID NO:386)	<b>D</b> <b>G</b> <b>K</b> <b>G</b> HYNPSLKS (SEQ ID NO:392)
DDK <b>G</b> HYNPSL <b>KD</b> (SEQ ID NO:387)	<b>D</b> <b>G</b> <b>K</b> <b>G</b> HYNPSL <b>KD</b> (SEQ ID NO:393)
DDK <b>G</b> SYNPSLKS (SEQ ID NO:388)	<b>D</b> <b>G</b> <b>K</b> <b>G</b> SYNPSLKS (SEQ ID NO:394)
DDK <b>G</b> SYNPSL <b>KD</b> (SEQ ID NO:389)	<b>D</b> <b>G</b> <b>K</b> <b>G</b> SYNPSL <b>KD</b> (SEQ ID NO:395)

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in palivizumab

**Table 3C - VH CDR3 Sequences**

NWYFDV (SEQ ID NO:3)	NWYFDV (SEQ ID NO:83)
<b>NFY</b> FDV (SEQ ID NO:12)	<b>NFY</b> FDV (SEQ ID NO:29)
NWYFDV (SEQ ID NO:94)	NWYFDV (SEQ ID NO:79)
<b>NFY</b> FDV (SEQ ID NO:97)	<b>NFY</b> FDV (SEQ ID NO:20)

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in palivizumab

Table 3D - VL CDR1 Sequences

KCQLSVGYMH (SEQ ID NO:4)	SCQLSVGYMH (SEQ ID NO:127)	LCQLSVGYMH (SEQ ID NO:204)
RVGYMH (SEQ ID NO:87)	RVGYMH (SEQ ID NO:132)	RVGYMH (SEQ ID NO:206)
KCQLFVGYMH (SEQ ID NO:396)	SCQLFVGYMH (SEQ ID NO:436)	LCQLFVGYMH (SEQ ID NO:476)
KCQSSVGYMH (SEQ ID NO:80)	SCQSSVGYMH (SEQ ID NO:129)	LCQSSVGYMH (SEQ ID NO:205)
KCQSRVGYMH (SEQ ID NO:84)	SCQSRVGYMH (SEQ ID NO:130)	LCQSRVGYMH (SEQ ID NO:203)
KCQSFVGYMH (SEQ ID NO:397)	SCQSFVGYMH (SEQ ID NO:437)	LCQSFVGYMH (SEQ ID NO:477)
KCQVSVGYMH (SEQ ID NO:398)	SCQVSVGYMH (SEQ ID NO:438)	LCQVSVGYMH (SEQ ID NO:478)
KCQVRVGYMH (SEQ ID NO:399)	SCQVRVGYMH (SEQ ID NO:439)	LCQVRVGYMH (SEQ ID NO:479)
KCQVFFVGYMH (SEQ ID NO:400)	SCQVFFVGYMH (SEQ ID NO:440)	LCQVFFVGYMH (SEQ ID NO:480)
KCSLSVGYMH (SEQ ID NO:112)	SCSLSVGYMH (SEQ ID NO:142)	LCSLSVGYMH (SEQ ID NO:196)
KCSLRVGYMH (SEQ ID NO:119)	SCSLRVGYMH (SEQ ID NO:148)	LCSLRVGYMH (SEQ ID NO:198)
KCSLFFVGYMH (SEQ ID NO:401)	SCSLFFVGYMH (SEQ ID NO:441)	LCSLFFVGYMH (SEQ ID NO:481)
KCSSSVGYMH (SEQ ID NO:115)	SCSSSVGYMH (SEQ ID NO:144)	LCSSSVGYMH (SEQ ID NO:197)
KCSSRVGYMH (SEQ ID NO:117)	SCSSRVGYMH (SEQ ID NO:146)	LCSSRVGYMH (SEQ ID NO:195)
KCSSFFVGYMH (SEQ ID NO:402)	SCSSFFVGYMH (SEQ ID NO:442)	LCSSFFVGYMH (SEQ ID NO:482)
KCSVSVGYMH (SEQ ID NO:403)	SCSVSVGYMH (SEQ ID NO:443)	LCSVSVGYMH (SEQ ID NO:483)
KCSVRVGYMH (SEQ ID NO:404)	SCSVRVGYMH (SEQ ID NO:444)	LCSVRVGYMH (SEQ ID NO:484)
KCSVFFVGYMH (SEQ ID NO:405)	SCSVFFVGYMH (SEQ ID NO:445)	LCSVFFVGYMH (SEQ ID NO:485)
KAQLSVGYMH (SEQ ID NO:182)	SAQLSVGYMH (SEQ ID NO:207)	LAQLSVGYMH (SEQ ID NO:486)
KAQLRVGYMH (SEQ ID NO:180)	SAQLRVGYMH (SEQ ID NO:190)	LAQLRVGYMH (SEQ ID NO:487)
KAQLFVGYMH (SEQ ID NO:406)	SAQLFVGYMH (SEQ ID NO:446)	LAQLFVGYMH (SEQ ID NO:488)
KAQSSVGYMH (SEQ ID NO:181)	SAQSSVGYMH (SEQ ID NO:191)	LAQSSVGYMH (SEQ ID NO:489)
KAQSRVGYMH (SEQ ID NO:179)	SAQSRVGYMH (SEQ ID NO:189)	LAQSRVGYMH (SEQ ID NO:490)
KAQSFVGYMH (SEQ ID NO:407)	SAQSFVGYMH (SEQ ID NO:447)	LAQSFVGYMH (SEQ ID NO:491)
KAQVSVGYMH (SEQ ID NO:408)	SAQVSVGYMH (SEQ ID NO:448)	LAQVSVGYMH (SEQ ID NO:492)
KAQVRVGYMH (SEQ ID NO:409)	SAQVRVGYMH (SEQ ID NO:449)	LAQVRVGYMH (SEQ ID NO:493)
KAQVFFVGYMH (SEQ ID NO:410)	SAQVFFVGYMH (SEQ ID NO:450)	LAQVFFVGYMH (SEQ ID NO:494)
KASLSVGYMH (SEQ ID NO:186)	SASLSVGYMH (SEQ ID NO:188)	LASLSVGYMH (SEQ ID NO:495)
KASLRVGYMH (SEQ ID NO:184)	SASLRVGYMH (SEQ ID NO:187)	LASLRVGYMH (SEQ ID NO:496)
KASLFFVGYMH (SEQ ID NO:411)	SASLFFVGYMH (SEQ ID NO:451)	LASLFFVGYMH (SEQ ID NO:497)
KASSSVGYMH (SEQ ID NO:185)	SASSSVGYMH (SEQ ID NO:14)	LASSSVGYMH (SEQ ID NO:498)

<b>KASSR</b> VGMYH (SEQ ID NO: 183)	<b>SASSR</b> VGMYH (SEQ ID NO: 39)	<b>LASSR</b> VGMYH (SEQ ID NO: 499)
<b>KASSF</b> VGMYH (SEQ ID NO: 412)	<b>SASSF</b> VGMYH (SEQ ID NO: 452)	<b>LASSF</b> VGMYH (SEQ ID NO: 500)
<b>KASVS</b> VGMYH (SEQ ID NO: 413)	<b>SASVS</b> VGMYH (SEQ ID NO: 453)	<b>LASVS</b> VGMYH (SEQ ID NO: 501)
<b>KASVR</b> VGMYH (SEQ ID NO: 414)	<b>SASVR</b> VGMYH (SEQ ID NO: 454)	<b>LASVR</b> VGMYH (SEQ ID NO: 502)
<b>KASVF</b> VGMYH (SEQ ID NO: 415)	<b>SASVF</b> VGMYH (SEQ ID NO: 455)	<b>LASVF</b> VGMYH (SEQ ID NO: 503)
<b>KLQLS</b> VGMYH (SEQ ID NO: 89)	<b>SLQLS</b> VGMYH (SEQ ID NO: 134)	<b>LLQLS</b> VGMYH (SEQ ID NO: 504)
<b>KLQLR</b> VGMYH (SEQ ID NO: 98)	<b>SLQLR</b> VGMYH (SEQ ID NO: 140)	<b>LLQLR</b> VGMYH (SEQ ID NO: 505)
<b>KLQLF</b> VGMYH (SEQ ID NO: 416)	<b>SLQLF</b> VGMYH (SEQ ID NO: 456)	<b>LLQLF</b> VGMYH (SEQ ID NO: 506)
<b>KLQSS</b> VGMYH (SEQ ID NO: 92)	<b>SLQSS</b> VGMYH (SEQ ID NO: 136)	<b>LLQSS</b> VGMYH (SEQ ID NO: 507)
<b>KLQSR</b> VGMYH (SEQ ID NO: 95)	<b>SLQSR</b> VGMYH (SEQ ID NO: 138)	<b>LLQSR</b> VGMYH (SEQ ID NO: 508)
<b>KLQSF</b> VGMYH (SEQ ID NO: 417)	<b>SLQSF</b> VGMYH (SEQ ID NO: 457)	<b>LLQSF</b> VGMYH (SEQ ID NO: 509)
<b>KLQVS</b> VGMYH (SEQ ID NO: 418)	<b>SLQVS</b> VGMYH (SEQ ID NO: 458)	<b>LLQVS</b> VGMYH (SEQ ID NO: 510)
<b>KLQVR</b> VGMYH (SEQ ID NO: 419)	<b>SLQVR</b> VGMYH (SEQ ID NO: 459)	<b>LLQVR</b> VGMYH (SEQ ID NO: 511)
<b>KLQVF</b> VGMYH (SEQ ID NO: 420)	<b>SLQVF</b> VGMYH (SEQ ID NO: 460)	<b>LLQVF</b> VGMYH (SEQ ID NO: 512)
<b>KLSSL</b> VGMYH (SEQ ID NO: 101)	<b>SLSSL</b> VGMYH (SEQ ID NO: 120)	<b>LLSSL</b> VGMYH (SEQ ID NO: 513)
<b>KLSLR</b> VGMYH (SEQ ID NO: 110)	<b>SLSLR</b> VGMYH (SEQ ID NO: 125)	<b>LLSLR</b> VGMYH (SEQ ID NO: 514)
<b>KLSLF</b> VGMYH (SEQ ID NO: 421)	<b>SLSLF</b> VGMYH (SEQ ID NO: 461)	<b>LLSLF</b> VGMYH (SEQ ID NO: 515)
<b>KLSSS</b> VGMYH (SEQ ID NO: 104)	<b>SLSSS</b> VGMYH (SEQ ID NO: 122)	<b>LLSSS</b> VGMYH (SEQ ID NO: 516)
<b>KLSSR</b> VGMYH (SEQ ID NO: 107)	<b>SLSSR</b> VGMYH (SEQ ID NO: 22)	<b>LLSSR</b> VGMYH (SEQ ID NO: 517)
<b>KLSSF</b> VGMYH (SEQ ID NO: 422)	<b>SLSSF</b> VGMYH (SEQ ID NO: 462)	<b>LLSSF</b> VGMYH (SEQ ID NO: 518)
<b>KLVS</b> VGMYH (SEQ ID NO: 423)	<b>SLVS</b> VGMYH (SEQ ID NO: 463)	<b>LLVS</b> VGMYH (SEQ ID NO: 519)
<b>KLSVR</b> VGMYH (SEQ ID NO: 424)	<b>SLSVR</b> VGMYH (SEQ ID NO: 464)	<b>LLSVR</b> VGMYH (SEQ ID NO: 520)
<b>KLSVF</b> VGMYH (SEQ ID NO: 425)	<b>SLSVF</b> VGMYH (SEQ ID NO: 465)	<b>LLSVF</b> VGMYH (SEQ ID NO: 521)
<b>KPQLS</b> VGMYH (SEQ ID NO: 163)	<b>SPQLS</b> VGMYH (SEQ ID NO: 177)	<b>LPQLS</b> VGMYH (SEQ ID NO: 200)
<b>KPQLR</b> VGMYH (SEQ ID NO: 159)	<b>SPQLR</b> VGMYH (SEQ ID NO: 173)	<b>LPQLR</b> VGMYH (SEQ ID NO: 202)
<b>KPQLF</b> VGMYH (SEQ ID NO: 426)	<b>SPQLF</b> VGMYH (SEQ ID NO: 466)	<b>LPQLF</b> VGMYH (SEQ ID NO: 522)
<b>KPQSS</b> VGMYH (SEQ ID NO: 161)	<b>SPQSS</b> VGMYH (SEQ ID NO: 176)	<b>LPQSS</b> VGMYH (SEQ ID NO: 201)
<b>KPQSR</b> VGMYH (SEQ ID NO: 157)	<b>SPQSR</b> VGMYH (SEQ ID NO: 171)	<b>LPQSR</b> VGMYH (SEQ ID NO: 199)
<b>KPQSF</b> VGMYH (SEQ ID NO: 427)	<b>SPQSF</b> VGMYH (SEQ ID NO: 467)	<b>LPQSF</b> VGMYH (SEQ ID NO: 523)
<b>KPQVS</b> VGMYH (SEQ ID NO: 428)	<b>SPQVS</b> VGMYH (SEQ ID NO: 468)	<b>LPQVS</b> VGMYH (SEQ ID NO: 524)
<b>KPQVR</b> VGMYH (SEQ ID NO: 429)	<b>SPQVR</b> VGMYH (SEQ ID NO: 469)	<b>LPQVR</b> VGMYH (SEQ ID NO: 525)

KPQVFVG <del>Y</del> MH (SEQ ID NO:430)	SPQVFVG <del>Y</del> MH (SEQ ID NO:470)	LPQVFVG <del>Y</del> MH (SEQ ID NO:526)
KPSLSVG <del>Y</del> MH (SEQ ID NO:155)	SPSLSVG <del>Y</del> MH (SEQ ID NO:169)	LPSLSVG <del>Y</del> MH (SEQ ID NO:192)
KPSLRVG <del>Y</del> MH (SEQ ID NO:152)	SPSLRVG <del>Y</del> MH (SEQ ID NO:166)	LPSLRVG <del>Y</del> MH (SEQ ID NO:194)
KPSLFVG <del>Y</del> MH (SEQ ID NO:431)	SPSLFVG <del>Y</del> MH (SEQ ID NO:471)	LPSLFVG <del>Y</del> MH (SEQ ID NO:527)
KPSSSVG <del>Y</del> MH (SEQ ID NO:153)	SPSSSVG <del>Y</del> MH (SEQ ID NO:168)	LPSSSVG <del>Y</del> MH (SEQ ID NO:193)
KPSSRVG <del>Y</del> MH (SEQ ID NO:150)	SPSSRVG <del>Y</del> MH (SEQ ID NO:31)	LPSSRVG <del>Y</del> MH (SEQ ID NO:47)
KPSSFVG <del>Y</del> MH (SEQ ID NO:432)	SPSSFVG <del>Y</del> MH (SEQ ID NO:472)	LPSFVG <del>Y</del> MH (SEQ ID NO:528)
KPSVSVG <del>Y</del> MH (SEQ ID NO:433)	SPSVSVG <del>Y</del> MH (SEQ ID NO:473)	LPSVSVG <del>Y</del> MH (SEQ ID NO:529)
KPSVRVG <del>Y</del> MH (SEQ ID NO:434)	SPSVRVG <del>Y</del> MH (SEQ ID NO:474)	LPSVRVG <del>Y</del> MH (SEQ ID NO:530)
KPSVFVG <del>Y</del> MH (SEQ ID NO:435)	SPSVFVG <del>Y</del> MH (SEQ ID NO:475)	LPSVFVG <del>Y</del> MH (SEQ ID NO:531)

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in palvizumab

Table 3E - VL CDR2 Sequences

DTSKLAS (SEQ ID NO:5)	DTFKLAS (SEQ ID NO:15)	DTYKLAS (SEQ ID NO:799)	DTRKLAS (SEQ ID NO:113&174)	DTMKLAS (SEQ ID NO:121&162)	DTKKLAS (SEQ ID NO:1211)	DTLKLAS (SEQ ID NO:135)
DTSKLSS (SEQ ID NO:165)	DTFKLSS (SEQ ID NO:96)	DTYKLSS (SEQ ID NO:800)	DTRKLSS (SEQ ID NO:175)	DTMKLSS (SEQ ID NO:164)	DTKKLSS (SEQ ID NO:1212)	DTLKLSS (SEQ ID NO:1355)
DTSKLKS (SEQ ID NO:532)	DTFKLKS (SEQ ID NO:660)	DTYKLKS (SEQ ID NO:801)	DTRKLKS (SEQ ID NO:943)	DTMKLKS (SEQ ID NO:1076)	DTKKLKS (SEQ ID NO:1213)	DTLKLKS (SEQ ID NO:1356)
DTSKLRS (SEQ ID NO:533)	DTFKLRS (SEQ ID NO:661)	DTYKLRS (SEQ ID NO:802)	DTRKLRS (SEQ ID NO:944)	DTMKLRS (SEQ ID NO:1077)	DTKKLRS (SEQ ID NO:1214)	DTLKLRS (SEQ ID NO:1357)
DTSKLHS (SEQ ID NO:534)	DTFKLHS (SEQ ID NO:662)	DTYKLHS (SEQ ID NO:803)	DTRKLHS (SEQ ID NO:945)	DTMKLHS (SEQ ID NO:1078)	DTKKLHS (SEQ ID NO:1215)	DTLKLHS (SEQ ID NO:1358)
DTSKLPS (SEQ ID NO:102)	DTFKLPS (SEQ ID NO:663)	DTYKLPS (SEQ ID NO:804)	DTRKLPS (SEQ ID NO:118)	DTMKLPS (SEQ ID NO:1079)	DTKKLPS (SEQ ID NO:1216)	DTLKLPS (SEQ ID NO:1359)



DTSKLTS (SEQ ID NO:535)	DTFKLTS (SEQ ID NO:664)	DTYKLT (SEQ ID NO:805)	DTRKLT (SEQ ID NO:946)	DTMKLT (SEQ ID NO:1080)	DTKKLT (SEQ ID NO:1217)	DTLKLTS (SEQ ID NO:1360)
DTSKLDS (SEQ ID NO:128)	DTFKLDS (SEQ ID NO:665)	DTYKLD (SEQ ID NO:806)	DTRKLD (SEQ ID NO:947)	DTMKLD (SEQ ID NO:1081)	DTKKLD (SEQ ID NO:1218)	DTLKLDS (SEQ ID NO:131)
DTSKHAS (SEQ ID NO:536)	DTFKHAS (SEQ ID NO:666)	DTYKHAS (SEQ ID NO:807)	DTRKHAS (SEQ ID NO:948)	DTMKHAS (SEQ ID NO:1082)	DTKKHAS (SEQ ID NO:1219)	DTLKHAS (SEQ ID NO:1361)
DTSKHSS (SEQ ID NO:537)	DTFKHSS (SEQ ID NO:667)	DTYKHSS (SEQ ID NO:808)	DTRKHSS (SEQ ID NO:949)	DTMKHSS (SEQ ID NO:1083)	DTKKHSS (SEQ ID NO:1220)	DTLKHSS (SEQ ID NO:1362)
DTSKHKS (SEQ ID NO:538)	DTFKHKS (SEQ ID NO:668)	DTYKHKS (SEQ ID NO:809)	DTRKHKS (SEQ ID NO:950)	DTMKHKS (SEQ ID NO:1084)	DTKKHKS (SEQ ID NO:1221)	DTLKHKS (SEQ ID NO:1363)
DTSKHRS (SEQ ID NO:539)	DTFKHRS (SEQ ID NO:669)	DTYKHRS (SEQ ID NO:810)	DTRKHRS (SEQ ID NO:951)	DTMKHRS (SEQ ID NO:1085)	DTKKHRS (SEQ ID NO:1222)	DTLKHRS (SEQ ID NO:1364)
DTSKHHS (SEQ ID NO:540)	DTFKHHS (SEQ ID NO:670)	DTYKHHS (SEQ ID NO:811)	DTRKHHS (SEQ ID NO:952)	DTMKHHS (SEQ ID NO:1086)	DTKKHHS (SEQ ID NO:1223)	DTLKHHS (SEQ ID NO:1365)
DTSKHPS (SEQ ID NO:541)	DTFKHPS (SEQ ID NO:671)	DTYKHPS (SEQ ID NO:812)	DTRKHPS (SEQ ID NO:953)	DTMKHPS (SEQ ID NO:1087)	DTKKHPS (SEQ ID NO:1224)	DTLKHPS (SEQ ID NO:1366)
DTSKHTS (SEQ ID NO:542)	DTFKHTS (SEQ ID NO:672)	DTYKHTS (SEQ ID NO:813)	DTRKHTS (SEQ ID NO:954)	DTMKHTS (SEQ ID NO:1088)	DTKKHTS (SEQ ID NO:1225)	DTLKHTS (SEQ ID NO:1367)
DTSKHDS (SEQ ID NO:543)	DTFKHDS (SEQ ID NO:673)	DTYKHDS (SEQ ID NO:814)	DTRKHDS (SEQ ID NO:955)	DTMKHDS (SEQ ID NO:1089)	DTKKHDS (SEQ ID NO:1226)	DTLKHDS (SEQ ID NO:1368)
DTSKQAS (SEQ ID NO:139)	DTFKQAS (SEQ ID NO:674)	DTYKQAS (SEQ ID NO:815)	DTRKQAS (SEQ ID NO:170)	DTMKQAS (SEQ ID NO:154)	DTKKQAS (SEQ ID NO:1227)	DTLKQAS (SEQ ID NO:1369)

DTSKQSS (SEQ ID NO:141)	DTFKQSS (SEQ ID NO:675)	DTYKQSS (SEQ ID NO:816)	DTRKQSS (SEQ ID NO:172)	DTMKQSS (SEQ ID NO:156)	DTKKQSS (SEQ ID NO:1228)	DTLKQSS (SEQ ID NO:1370)
DTSKQKS (SEQ ID NO:544)	DTFKQKS (SEQ ID NO:676)	DTYKQKS (SEQ ID NO:817)	DTRKQKS (SEQ ID NO:956)	DTMKQKS (SEQ ID NO:1090)	DTKKQKS (SEQ ID NO:1229)	DTLKQKS (SEQ ID NO:1371)
DTSKQRS (SEQ ID NO:545)	DTFKQRS (SEQ ID NO:677)	DTYQRS (SEQ ID NO:818)	DTRQRS (SEQ ID NO:957)	DTMKQRS (SEQ ID NO:1091)	DTKKQRS (SEQ ID NO:1230)	DTLKQRS (SEQ ID NO:1372)
DTSKQHS (SEQ ID NO:546)	DTFKQHS (SEQ ID NO:678)	DTYQHS (SEQ ID NO:819)	DTRQHS (SEQ ID NO:958)	DTMKQHS (SEQ ID NO:1092)	DTKKQHS (SEQ ID NO:1231)	DTLKQHS (SEQ ID NO:1373)
DTSKQPS (SEQ ID NO:547)	DTFKQPS (SEQ ID NO:679)	DTYQPS (SEQ ID NO:820)	DTRQPS (SEQ ID NO:959)	DTMKQPS (SEQ ID NO:1093)	DTKKQPS (SEQ ID NO:1232)	DTLKQPS (SEQ ID NO:1374)
DTSKQTS (SEQ ID NO:548)	DTFKQTS (SEQ ID NO:680)	DTYQTS (SEQ ID NO:821)	DTRQTS (SEQ ID NO:960)	DTMKQTS (SEQ ID NO:1094)	DTKKQTS (SEQ ID NO:1233)	DTLKQTS (SEQ ID NO:1375)
DTSKQDS (SEQ ID NO:549)	DTFKQDS (SEQ ID NO:681)	DTYQDS (SEQ ID NO:822)	DTRQDS (SEQ ID NO:961)	DTMKQDS (SEQ ID NO:1095)	DTKKQDS (SEQ ID NO:1234)	DTLKQDS (SEQ ID NO:1376)
DTSGLAS (SEQ ID NO:105)	DTFGLAS (SEQ ID NO:682)	DTYGLAS (SEQ ID NO:823)	DTRGLAS (SEQ ID NO:116)	DTMGLAS (SEQ ID NO:1096)	DTKGLAS (SEQ ID NO:1235)	DTLGLAS (SEQ ID NO:1377)
DTSGLSS (SEQ ID NO:550)	DTFGLSS (SEQ ID NO:683)	DTYGLSS (SEQ ID NO:824)	DTRGLSS (SEQ ID NO:962)	DTMGLSS (SEQ ID NO:1097)	DTKGLSS (SEQ ID NO:1236)	DTLGLSS (SEQ ID NO:1378)
DTSGLKS (SEQ ID NO:551)	DTFGLKS (SEQ ID NO:684)	DTYGLKS (SEQ ID NO:825)	DTRGLKS (SEQ ID NO:963)	DTMGLKS (SEQ ID NO:1098)	DTKGLKS (SEQ ID NO:1237)	DTLGLKS (SEQ ID NO:1379)
DTSGLRS (SEQ ID NO:552)	DTFGLRS (SEQ ID NO:685)	DTYGLRS (SEQ ID NO:826)	DTRGLRS (SEQ ID NO:964)	DTMGLRS (SEQ ID NO:1099)	DTKGLRS (SEQ ID NO:1238)	DTLGLRS (SEQ ID NO:1380)

DTSG $\overline{\text{LH}}$ S (SEQ ID NO:553)	DTFGL $\overline{\text{H}}$ S (SEQ ID NO:686)	DTYGL $\overline{\text{H}}$ S (SEQ ID NO:827)	DTRGL $\overline{\text{H}}$ S (SEQ ID NO:965)	DTMGL $\overline{\text{H}}$ S (SEQ ID NO:1100)	DTKGL $\overline{\text{H}}$ S (SEQ ID NO:1239)	DTLGL $\overline{\text{H}}$ S (SEQ ID NO:1381)
DTSG $\overline{\text{LP}}$ S (SEQ ID NO:108)	DTFGL $\overline{\text{P}}$ S (SEQ ID NO:687)	DTYGL $\overline{\text{P}}$ S (SEQ ID NO:828)	DTRGL $\overline{\text{P}}$ S (SEQ ID NO:27)	DTMGL $\overline{\text{P}}$ S (SEQ ID NO:1101)	DTKGL $\overline{\text{P}}$ S (SEQ ID NO:1240)	DTLGL $\overline{\text{P}}$ S (SEQ ID NO:1382)
DTSG $\overline{\text{LT}}$ S (SEQ ID NO:554)	DTFGL $\overline{\text{T}}$ S (SEQ ID NO:688)	DTYGL $\overline{\text{T}}$ S (SEQ ID NO:829)	DTRGL $\overline{\text{T}}$ S (SEQ ID NO:966)	DTMGL $\overline{\text{T}}$ S (SEQ ID NO:1102)	DTKGL $\overline{\text{T}}$ S (SEQ ID NO:1241)	DTLGL $\overline{\text{T}}$ S (SEQ ID NO:1383)
DTSG $\overline{\text{LD}}$ S (SEQ ID NO:555)	DTFGL $\overline{\text{D}}$ S (SEQ ID NO:689)	DTYGL $\overline{\text{D}}$ S (SEQ ID NO:830)	DTRGL $\overline{\text{D}}$ S (SEQ ID NO:967)	DTMGL $\overline{\text{D}}$ S (SEQ ID NO:1103)	DTKGL $\overline{\text{D}}$ S (SEQ ID NO:1242)	DTLGL $\overline{\text{D}}$ S (SEQ ID NO:1384)
DTSG $\overline{\text{HA}}$ S (SEQ ID NO:556)	DTFGL $\overline{\text{A}}$ S (SEQ ID NO:690)	DTYGL $\overline{\text{A}}$ S (SEQ ID NO:831)	DTRGL $\overline{\text{A}}$ S (SEQ ID NO:968)	DTMGL $\overline{\text{A}}$ S (SEQ ID NO:1104)	DTKGL $\overline{\text{A}}$ S (SEQ ID NO:1243)	DTLGL $\overline{\text{A}}$ S (SEQ ID NO:1385)
DTSG $\overline{\text{HS}}$ (SEQ ID NO:557)	DTFGL $\overline{\text{S}}$ (SEQ ID NO:691)	DTYGL $\overline{\text{S}}$ (SEQ ID NO:832)	DTRGL $\overline{\text{S}}$ (SEQ ID NO:969)	DTMGL $\overline{\text{S}}$ (SEQ ID NO:1105)	DTKGL $\overline{\text{S}}$ (SEQ ID NO:1244)	DTLGL $\overline{\text{S}}$ (SEQ ID NO:1386)
DTSG $\overline{\text{HK}}$ S (SEQ ID NO:558)	DTFGL $\overline{\text{K}}$ S (SEQ ID NO:692)	DTYGL $\overline{\text{K}}$ S (SEQ ID NO:833)	DTRGL $\overline{\text{K}}$ S (SEQ ID NO:970)	DTMGL $\overline{\text{K}}$ S (SEQ ID NO:1106)	DTKGL $\overline{\text{K}}$ S (SEQ ID NO:1245)	DTLGL $\overline{\text{K}}$ S (SEQ ID NO:1387)
DTSG $\overline{\text{HR}}$ S (SEQ ID NO:559)	DTFGL $\overline{\text{R}}$ S (SEQ ID NO:693)	DTYGL $\overline{\text{R}}$ S (SEQ ID NO:834)	DTRGL $\overline{\text{R}}$ S (SEQ ID NO:971)	DTMGL $\overline{\text{R}}$ S (SEQ ID NO:1107)	DTKGL $\overline{\text{R}}$ S (SEQ ID NO:1246)	DTLGL $\overline{\text{R}}$ S (SEQ ID NO:1388)
DTSG $\overline{\text{HH}}$ S (SEQ ID NO:560)	DTFGL $\overline{\text{H}}$ S (SEQ ID NO:694)	DTYGL $\overline{\text{H}}$ S (SEQ ID NO:835)	DTRGL $\overline{\text{H}}$ S (SEQ ID NO:972)	DTMGL $\overline{\text{H}}$ S (SEQ ID NO:1108)	DTKGL $\overline{\text{H}}$ S (SEQ ID NO:1247)	DTLGL $\overline{\text{H}}$ S (SEQ ID NO:1389)
DTSG $\overline{\text{HP}}$ S (SEQ ID NO:561)	DTFGL $\overline{\text{P}}$ S (SEQ ID NO:695)	DTYGL $\overline{\text{P}}$ S (SEQ ID NO:836)	DTRGL $\overline{\text{P}}$ S (SEQ ID NO:973)	DTMGL $\overline{\text{P}}$ S (SEQ ID NO:1109)	DTKGL $\overline{\text{P}}$ S (SEQ ID NO:1248)	DTLGL $\overline{\text{P}}$ S (SEQ ID NO:1390)
DTSG $\overline{\text{HT}}$ S (SEQ ID NO:562)	DTFGL $\overline{\text{T}}$ S (SEQ ID NO:696)	DTYGL $\overline{\text{T}}$ S (SEQ ID NO:837)	DTRGL $\overline{\text{T}}$ S (SEQ ID NO:974)	DTMGL $\overline{\text{T}}$ S (SEQ ID NO:1110)	DTKGL $\overline{\text{T}}$ S (SEQ ID NO:1249)	DTLGL $\overline{\text{T}}$ S (SEQ ID NO:1391)

DTSGHDS (SEQ ID NO:563)	DTFGHDS (SEQ ID NO:697)	DTYGHDS (SEQ ID NO:838)	DTRGHDS (SEQ ID NO:975)	DTMGHDS (SEQ ID NO:1111)	DTKGHDS (SEQ ID NO:1250)	DTLGHDS (SEQ ID NO:1392)
DTSGQAS (SEQ ID NO:564)	DTFGQAS (SEQ ID NO:698)	DTYQAS (SEQ ID NO:839)	DTRQAS (SEQ ID NO:976)	DTMQAS (SEQ ID NO:1112)	DTKQAS (SEQ ID NO:1251)	DTLQAS (SEQ ID NO:1393)
DTSGQSS (SEQ ID NO:565)	DTFGQSS (SEQ ID NO:699)	DTYQSS (SEQ ID NO:840)	DTRQSS (SEQ ID NO:977)	DTMQSS (SEQ ID NO:1113)	DTKQSS (SEQ ID NO:1252)	DTLQSS (SEQ ID NO:1394)
DTSGQKS (SEQ ID NO:566)	DTFGQKS (SEQ ID NO:700)	DTYQKS (SEQ ID NO:841)	DTRQKS (SEQ ID NO:978)	DTMQKS (SEQ ID NO:1114)	DTKQKS (SEQ ID NO:1253)	DTLQKS (SEQ ID NO:1395)
DTSGQRS (SEQ ID NO:567)	DTFGQRS (SEQ ID NO:701)	DTYQRS (SEQ ID NO:842)	DTRQRS (SEQ ID NO:979)	DTMQRS (SEQ ID NO:1115)	DTKQRS (SEQ ID NO:1254)	DTLQRS (SEQ ID NO:1396)
DTSGQHS (SEQ ID NO:568)	DTFGQHS (SEQ ID NO:702)	DTYQHS (SEQ ID NO:843)	DTRQHS (SEQ ID NO:980)	DTMQHS (SEQ ID NO:1116)	DTKQHS (SEQ ID NO:1255)	DTLQHS (SEQ ID NO:1397)
DTSGQPS (SEQ ID NO:569)	DTFGQPS (SEQ ID NO:703)	DTYQPS (SEQ ID NO:844)	DTRQPS (SEQ ID NO:981)	DTMQPS (SEQ ID NO:1117)	DTKQPS (SEQ ID NO:1256)	DTLQPS (SEQ ID NO:1398)
DTSGQTS (SEQ ID NO:570)	DTFGQTS (SEQ ID NO:704)	DTYQTS (SEQ ID NO:845)	DTRQTS (SEQ ID NO:982)	DTMQTS (SEQ ID NO:1118)	DTKQTS (SEQ ID NO:1257)	DTLQTS (SEQ ID NO:1399)
DTSGQDS (SEQ ID NO:571)	DTFGQDS (SEQ ID NO:705)	DTYQDS (SEQ ID NO:846)	DTRQDS (SEQ ID NO:983)	DTMQDS (SEQ ID NO:1119)	DTKQDS (SEQ ID NO:1258)	DTLQDS (SEQ ID NO:1400)
DTSRLLAS (SEQ ID NO:123)	DTFRLLAS (SEQ ID NO:706)	DTYRLAS (SEQ ID NO:847)	DTRRLAS (SEQ ID NO:984)	DTMRLAS (SEQ ID NO:1120)	DTKRLAS (SEQ ID NO:1259)	DTLRLAS (SEQ ID NO:1401)
DTSRLLSS (SEQ ID NO:572)	DTFRLLSS (SEQ ID NO:707)	DTYRLSS (SEQ ID NO:848)	DTRRLSS (SEQ ID NO:985)	DTMRLSS (SEQ ID NO:1120)	DTKRLSS (SEQ ID NO:1260)	DTLRLSS (SEQ ID NO:1402)

DTSRLKS (SEQ ID NO:573)	DTFRLKS (SEQ ID NO:708)	DTYRLKS (SEQ ID NO:849)	DTRRLKS (SEQ ID NO:986)	DTMRLKS (SEQ ID NO:1121)	DTKRLKS (SEQ ID NO:1261)	DTLRLKS (SEQ ID NO:1403)
DTSRLPS (SEQ ID NO:574)	DTFRLPS (SEQ ID NO:709)	DTYRLPS (SEQ ID NO:850)	DTRRLPS (SEQ ID NO:987)	DTMRLPS (SEQ ID NO:1122)	DTKRLPS (SEQ ID NO:1262)	DTLRLPS (SEQ ID NO:1404)
DTSRLHS (SEQ ID NO:575)	DTFRLHS (SEQ ID NO:710)	DTYRLHS (SEQ ID NO:851)	DTRRLHS (SEQ ID NO:988)	DTMRLHS (SEQ ID NO:1123)	DTKRLHS (SEQ ID NO:1263)	DTLRLHS (SEQ ID NO:1405)
DTSRLPS (SEQ ID NO:576)	DTFRLPS (SEQ ID NO:711)	DTYRLPS (SEQ ID NO:852)	DTRRLPS (SEQ ID NO:989)	DTMRLPS (SEQ ID NO:1124)	DTKRLPS (SEQ ID NO:1264)	DTLRLPS (SEQ ID NO:1406)
DTSRLTS (SEQ ID NO:577)	DTFRLTS (SEQ ID NO:712)	DTYRLTS (SEQ ID NO:853)	DTRRLTS (SEQ ID NO:990)	DTMRLTS (SEQ ID NO:1125)	DTKRLTS (SEQ ID NO:1265)	DTLRLTS (SEQ ID NO:1407)
DTSRLDS (SEQ ID NO:578)	DTFRLDS (SEQ ID NO:713)	DTYRLDS (SEQ ID NO:854)	DTRRLDS (SEQ ID NO:991)	DTMRLDS (SEQ ID NO:1126)	DTKRLDS (SEQ ID NO:1266)	DTLRLDS (SEQ ID NO:1408)
DTSRHAS (SEQ ID NO:579)	DTFRHAS (SEQ ID NO:714)	DTYRHAS (SEQ ID NO:855)	DTRRHAS (SEQ ID NO:992)	DTMRHAS (SEQ ID NO:1127)	DTKRHAS (SEQ ID NO:1267)	DTLRHAS (SEQ ID NO:1409)
DTSRHSS (SEQ ID NO:580)	DTFRHSS (SEQ ID NO:715)	DTYRHSS (SEQ ID NO:856)	DTRRHSS (SEQ ID NO:993)	DTMRHSS (SEQ ID NO:1128)	DTKRHSS (SEQ ID NO:1268)	DTLRHSS (SEQ ID NO:1410)
DTSRHKS (SEQ ID NO:581)	DTFRHKS (SEQ ID NO:716)	DTYRHKS (SEQ ID NO:857)	DTRRHKS (SEQ ID NO:994)	DTMRHKS (SEQ ID NO:1129)	DTKRHKS (SEQ ID NO:1269)	DTLRHKS (SEQ ID NO:1411)
DTSRHRS (SEQ ID NO:582)	DTFRHRS (SEQ ID NO:717)	DTYRHRS (SEQ ID NO:858)	DTRRHRS (SEQ ID NO:995)	DTMRHRS (SEQ ID NO:1130)	DTKRHRS (SEQ ID NO:1270)	DTLRHRS (SEQ ID NO:1412)
DTSRHHS (SEQ ID NO:583)	DTFRHHS (SEQ ID NO:718)	DTYRHHS (SEQ ID NO:859)	DTRRHHS (SEQ ID NO:996)	DTMRHHS (SEQ ID NO:1131)	DTKRHHS (SEQ ID NO:1271)	DTLRHHS (SEQ ID NO:1413)

<u>DTSRHPS</u> (SEQ ID NO:584)	<u>DTFRHPS</u> (SEQ ID NO:719)	<u>DTYRHPS</u> (SEQ ID NO:860)	<u>DTRRHPS</u> (SEQ ID NO:997)	<u>DTMRHPS</u> (SEQ ID NO:1132)	<u>DTKRHPS</u> (SEQ ID NO:1272)	<u>DTLRHPS</u> (SEQ ID NO:1414)
<u>DTSRHTS</u> (SEQ ID NO:585)	<u>DTFRHTS</u> (SEQ ID NO:720)	<u>DTYRHTS</u> (SEQ ID NO:861)	<u>DTRRHTS</u> (SEQ ID NO:998)	<u>DTMRHTS</u> (SEQ ID NO:1133)	<u>DTKRHTS</u> (SEQ ID NO:1273)	<u>DTLRHTS</u> (SEQ ID NO:1415)
<u>DTSRHDS</u> (SEQ ID NO:586)	<u>DTFRHDS</u> (SEQ ID NO:721)	<u>DTYRHDS</u> (SEQ ID NO:862)	<u>DTRRHDS</u> (SEQ ID NO:999)	<u>DTMRHDS</u> (SEQ ID NO:1134)	<u>DTKRHDS</u> (SEQ ID NO:1274)	<u>DTLRHDS</u> (SEQ ID NO:1416)
<u>DTSRQAS</u> (SEQ ID NO:587)	<u>DTFRQAS</u> (SEQ ID NO:722)	<u>DTYRQAS</u> (SEQ ID NO:863)	<u>DTRRQAS</u> (SEQ ID NO:1000)	<u>DTMRQAS</u> (SEQ ID NO:1135)	<u>DTKRQAS</u> (SEQ ID NO:1275)	<u>DTLRQAS</u> (SEQ ID NO:1417)
<u>DTSRQSS</u> (SEQ ID NO:588)	<u>DTFRQSS</u> (SEQ ID NO:723)	<u>DTYRQSS</u> (SEQ ID NO:864)	<u>DTRRQSS</u> (SEQ ID NO:1001)	<u>DTMRQSS</u> (SEQ ID NO:1136)	<u>DTKRQSS</u> (SEQ ID NO:1276)	<u>DTLRQSS</u> (SEQ ID NO:1418)
<u>DTSRQKS</u> (SEQ ID NO:589)	<u>DTFRQKS</u> (SEQ ID NO:724)	<u>DTYRQKS</u> (SEQ ID NO:865)	<u>DTRRQKS</u> (SEQ ID NO:1002)	<u>DTMRQKS</u> (SEQ ID NO:1137)	<u>DTKRQKS</u> (SEQ ID NO:1277)	<u>DTLRQKS</u> (SEQ ID NO:1419)
<u>DTSRQRS</u> (SEQ ID NO:590)	<u>DTFRQRS</u> (SEQ ID NO:725)	<u>DTYRQRS</u> (SEQ ID NO:866)	<u>DTRRQRS</u> (SEQ ID NO:1003)	<u>DTMRQRS</u> (SEQ ID NO:1138)	<u>DTKRQRS</u> (SEQ ID NO:1278)	<u>DTLRQRS</u> (SEQ ID NO:1420)
<u>DTSRQHS</u> (SEQ ID NO:591)	<u>DTFRQHS</u> (SEQ ID NO:726)	<u>DTYRQHS</u> (SEQ ID NO:867)	<u>DTRRQHS</u> (SEQ ID NO:1004)	<u>DTMRQHS</u> (SEQ ID NO:1139)	<u>DTKRQHS</u> (SEQ ID NO:1279)	<u>DTLRQHS</u> (SEQ ID NO:1421)
<u>DTSRQPS</u> (SEQ ID NO:592)	<u>DTFRQPS</u> (SEQ ID NO:727)	<u>DTYRQPS</u> (SEQ ID NO:868)	<u>DTRRQPS</u> (SEQ ID NO:1005)	<u>DTMRQPS</u> (SEQ ID NO:1140)	<u>DTKRQPS</u> (SEQ ID NO:1280)	<u>DTLRQPS</u> (SEQ ID NO:1422)
<u>DTSRQTS</u> (SEQ ID NO:593)	<u>DTFRQTS</u> (SEQ ID NO:728)	<u>DTYRQTS</u> (SEQ ID NO:869)	<u>DTRRQTS</u> (SEQ ID NO:1006)	<u>DTMRQTS</u> (SEQ ID NO:1141)	<u>DTKRQTS</u> (SEQ ID NO:1281)	<u>DTLRQTS</u> (SEQ ID NO:1423)
<u>DTSRQDS</u> (SEQ ID NO:594)	<u>DTFRQDS</u> (SEQ ID NO:729)	<u>DTYRQDS</u> (SEQ ID NO:870)	<u>DTRRQDS</u> (SEQ ID NO:1007)	<u>DTMRQDS</u> (SEQ ID NO:1142)	<u>DTKRQDS</u> (SEQ ID NO:1282)	<u>DTLRQDS</u> (SEQ ID NO:1424)

DTSYLAS (SEQ ID NOS:81&143)	DTFYLAS (SEQ ID NO:99)	DTYYLAS (SEQ ID NO:871)	DTRYLAS (SEQ ID NO:178)	DTMYLAS (SEQ ID NO:158)	DTKYLAS (SEQ ID NO:1283)	DTLYLAS (SEQ ID NO:1425)
DTSYLSS (SEQ ID NOS:85&145)	DTFYLSS (SEQ ID NO:90)	DTYYLSS (SEQ ID NO:872)	DTRYLSS (SEQ ID NO:59)	DTMYLSS (SEQ ID NO:160)	DTKYLSS (SEQ ID NO:1284)	DTLYLSS (SEQ ID NO:1426)
DTSYLKS (SEQ ID NO:595)	DTFYLKS (SEQ ID NO:730)	DTYYLKS (SEQ ID NO:873)	DTRYLKS (SEQ ID NO:1008)	DTMYLKS (SEQ ID NO:1143)	DTKYLKS (SEQ ID NO:1285)	DTLYLKS (SEQ ID NO:1427)
DTSYLRS (SEQ ID NO:596)	DTFYLRS (SEQ ID NO:731)	DTYYLRS (SEQ ID NO:874)	DTRYLRS (SEQ ID NO:1009)	DTMYLRS (SEQ ID NO:1144)	DTKYLRS (SEQ ID NO:1286)	DTLYLRS (SEQ ID NO:1428)
DTSYLHS (SEQ ID NO:597)	DTFYLHS (SEQ ID NO:732)	DTYYLHS (SEQ ID NO:875)	DTRYLHS (SEQ ID NO:1010)	DTMYLHS (SEQ ID NO:1145)	DTKYLHS (SEQ ID NO:1287)	DTLYLHS (SEQ ID NO:1429)
DTSYLPS (SEQ ID NO:598)	DTFYLPS (SEQ ID NO:733)	DTYYLPS (SEQ ID NO:876)	DTRYLPS (SEQ ID NO:1011)	DTMYLPS (SEQ ID NO:1146)	DTKYLPS (SEQ ID NO:1288)	DTLYLPS (SEQ ID NO:1430)
DTSYLTS (SEQ ID NO:599)	DTFYLTS (SEQ ID NO:734)	DTYYLTS (SEQ ID NO:877)	DTRYLTS (SEQ ID NO:1012)	DTMYLTS (SEQ ID NO:1147)	DTKYLTS (SEQ ID NO:1289)	DTLYLTS (SEQ ID NO:1431)
DTSYLDS (SEQ ID NO:600)	DTFYLDS (SEQ ID NO:735)	DTYYLDS (SEQ ID NO:878)	DTRYLDS (SEQ ID NO:1013)	DTMYLDS (SEQ ID NO:1148)	DTKYLDS (SEQ ID NO:1290)	DTLYLDS (SEQ ID NO:1432)
DTSYHAS (SEQ ID NO:601)	DTFYHAS (SEQ ID NO:736)	DTYYHAS (SEQ ID NO:879)	DTRYHAS (SEQ ID NO:1014)	DTMYHAS (SEQ ID NO:1149)	DTKYHAS (SEQ ID NO:1291)	DTLYHAS (SEQ ID NO:1433)
DTSYHSS (SEQ ID NO:602)	DTFYHSS (SEQ ID NO:737)	DTYYHSS (SEQ ID NO:880)	DTRYHSS (SEQ ID NO:1015)	DTMYHSS (SEQ ID NO:1150)	DTKYHSS (SEQ ID NO:1292)	DTLYHSS (SEQ ID NO:1434)
DTSYHKS (SEQ ID NO:603)	DTFYHKS (SEQ ID NO:738)	DTYYHKS (SEQ ID NO:881)	DTRYHKS (SEQ ID NO:1016)	DTMYHKS (SEQ ID NO:1151)	DTKYHKS (SEQ ID NO:1293)	DTLYHKS (SEQ ID NO:1435)

DTSYHRS (SEQ ID NO: 604)	DTFYHRS (SEQ ID NO: 739)	DTYYHRS (SEQ ID NO: 882)	DTRYHRS (SEQ ID NO: 1017)	DTMYHRS (SEQ ID NO: 1152)	DTKYHRS (SEQ ID NO: 1294)	DTLYHRS (SEQ ID NO: 1436)
DTSYHHS (SEQ ID NO: 605)	DTFYHHS (SEQ ID NO: 740)	DTYYHHS (SEQ ID NO: 883)	DTRYHHS (SEQ ID NO: 1018)	DTMYHHS (SEQ ID NO: 1153)	DTKYHHS (SEQ ID NO: 1295)	DTLYHHS (SEQ ID NO: 1437)
DTSYHPS (SEQ ID NO: 606)	DTFYHPS (SEQ ID NO: 741)	DTYYHPS (SEQ ID NO: 884)	DTRYHPS (SEQ ID NO: 1019)	DTMYHPS (SEQ ID NO: 1154)	DTKYHPS (SEQ ID NO: 1296)	DTLYHPS (SEQ ID NO: 1438)
DTSYHTS (SEQ ID NO: 607)	DTFYHTS (SEQ ID NO: 742)	DTYYHTS (SEQ ID NO: 885)	DTRYHTS (SEQ ID NO: 1020)	DTMYHTS (SEQ ID NO: 1155)	DTKYHTS (SEQ ID NO: 1297)	DTLYHTS (SEQ ID NO: 1439)
DTSYHDS (SEQ ID NO: 608)	DTFYHDS (SEQ ID NO: 743)	DTYYHDS (SEQ ID NO: 886)	DTRYHDS (SEQ ID NO: 1021)	DTMYHDS (SEQ ID NO: 1156)	DTKYHDS (SEQ ID NO: 1298)	DTLYHDS (SEQ ID NO: 1440)
DTSYQAS (SEQ ID NO: 147)	DTFYQAS (SEQ ID NO: 744)	DTYYQAS (SEQ ID NO: 887)	DTRYQAS (SEQ ID NO: 167)	DTMYQAS (SEQ ID NO: 151)	DTKYQAS (SEQ ID NO: 1299)	DTLYQAS (SEQ ID NO: 1441)
DTSYQSS (SEQ ID NO: 149)	DTFYQSS (SEQ ID NO: 745)	DTYYQSS (SEQ ID NO: 888)	DTRYQSS (SEQ ID NO: 53)	DTMYQSS (SEQ ID NO: 43)	DTKYQSS (SEQ ID NO: 1300)	DTLYQSS (SEQ ID NO: 1442)
DTSYQKS (SEQ ID NO: 609)	DTFYQKS (SEQ ID NO: 746)	DTYYQKS (SEQ ID NO: 889)	DTRYQKS (SEQ ID NO: 1022)	DTMYQKS (SEQ ID NO: 1157)	DTKYQKS (SEQ ID NO: 1301)	DTLYQKS (SEQ ID NO: 1443)
DTSYQRS (SEQ ID NO: 610)	DTFYQRS (SEQ ID NO: 747)	DTYYQRS (SEQ ID NO: 890)	DTRYQRS (SEQ ID NO: 1023)	DTMYQRS (SEQ ID NO: 1158)	DTKYQRS (SEQ ID NO: 1302)	DTLYQRS (SEQ ID NO: 1444)
DTSYQHS (SEQ ID NO: 611)	DTFYQHS (SEQ ID NO: 748)	DTYYQHS (SEQ ID NO: 891)	DTRYQHS (SEQ ID NO: 1024)	DTMYQHS (SEQ ID NO: 1159)	DTKYQHS (SEQ ID NO: 1303)	DTLYQHS (SEQ ID NO: 1445)
DTSYQPS (SEQ ID NO: 612)	DTFYQPS (SEQ ID NO: 749)	DTYYQPS (SEQ ID NO: 892)	DTRYQPS (SEQ ID NO: 1025)	DTMYQPS (SEQ ID NO: 1160)	DTKYQPS (SEQ ID NO: 1304)	DTLYQPS (SEQ ID NO: 1446)



DTSYQTS (SEQ ID NO:613)	DTFYQTS (SEQ ID NO:750)	DTYYQTS (SEQ ID NO:893)	DTRYQTS (SEQ ID NO:1026)	DTMYQTS (SEQ ID NO:1161)	DTKYQTS (SEQ ID NO:1305)	DTLYQTS (SEQ ID NO:1447)
DTSYQDS (SEQ ID NO:614)	DTFYQDS (SEQ ID NO:751)	DTYYQDS (SEQ ID NO:894)	DTRYQDS (SEQ ID NO:1027)	DTMYQDS (SEQ ID NO:1162)	DTKYQDS (SEQ ID NO:1306)	DTLYQDS (SEQ ID NO:1448)
DTSFILAS (SEQ ID NO:615)	DTFFILAS (SEQ ID NO:752)	DTYFILAS (SEQ ID NO:895)	DTRFILAS (SEQ ID NO:1028)	DTMFILAS (SEQ ID NO:1163)	DTKFILAS (SEQ ID NO:1307)	DTLFILAS (SEQ ID NO:1449)
DTSFILSS (SEQ ID NO:616)	DTFFILSS (SEQ ID NO:753)	DTYFILSS (SEQ ID NO:896)	DTRFILSS (SEQ ID NO:1029)	DTMFILSS (SEQ ID NO:1164)	DTKFILSS (SEQ ID NO:1308)	DTLFILSS (SEQ ID NO:1450)
DTSFILKS (SEQ ID NO:617)	DTFFILKS (SEQ ID NO:754)	DTYFILKS (SEQ ID NO:897)	DTRFILKS (SEQ ID NO:1030)	DTMFILKS (SEQ ID NO:1165)	DTKFILKS (SEQ ID NO:1309)	DTLFILKS (SEQ ID NO:1451)
DTSFILRS (SEQ ID NO:618)	DTFFILRS (SEQ ID NO:755)	DTYFILRS (SEQ ID NO:898)	DTRFILRS (SEQ ID NO:1031)	DTMFILRS (SEQ ID NO:1166)	DTKFILRS (SEQ ID NO:1310)	DTLFILRS (SEQ ID NO:1452)
DTSFILHS (SEQ ID NO:619)	DTFFILHS (SEQ ID NO:756)	DTYFILHS (SEQ ID NO:899)	DTRFILHS (SEQ ID NO:1032)	DTMFILHS (SEQ ID NO:1167)	DTKFILHS (SEQ ID NO:1311)	DTLFILHS (SEQ ID NO:1453)
DTSFILPS (SEQ ID NO:620)	DTFFILPS (SEQ ID NO:757)	DTYFILPS (SEQ ID NO:900)	DTRFILPS (SEQ ID NO:1033)	DTMFILPS (SEQ ID NO:1168)	DTKFILPS (SEQ ID NO:1312)	DTLFILPS (SEQ ID NO:1454)
DTSFILTS (SEQ ID NO:621)	DTFFILTS (SEQ ID NO:758)	DTYFILTS (SEQ ID NO:901)	DTRFILTS (SEQ ID NO:1034)	DTMFILTS (SEQ ID NO:1169)	DTKFILTS (SEQ ID NO:1313)	DTLFILTS (SEQ ID NO:1455)
DTSFILDS (SEQ ID NO:77)	DTFFILDS (SEQ ID NO:50)	DTYFILDS (SEQ ID NO:902)	DTRFILDS (SEQ ID NO:1035)	DTMFILDS (SEQ ID NO:1170)	DTKFILDS (SEQ ID NO:1314)	DTLFILDS (SEQ ID NO:1456)
DTSFHAS (SEQ ID NO:622)	DTFFHAS (SEQ ID NO:759)	DTYFHAS (SEQ ID NO:903)	DTRFHAS (SEQ ID NO:1036)	DTMFHAS (SEQ ID NO:1171)	DTKFHAS (SEQ ID NO:1315)	DTLFHAS (SEQ ID NO:1457)

DTSFHSS (SEQ ID NO: 623)	DTFFHSS (SEQ ID NO: 760)	DTYFHSS (SEQ ID NO: 904)	DTRFHSS (SEQ ID NO: 1037)	DTMFHSS (SEQ ID NO: 1172)	DTKFHSS (SEQ ID NO: 1316)	DTLFHSS (SEQ ID NO: 1458)
DTSFHKS (SEQ ID NO: 624)	DTFFHKS (SEQ ID NO: 761)	DTYFHKS (SEQ ID NO: 905)	DTRFHKS (SEQ ID NO: 1038)	DTMFHKS (SEQ ID NO: 1173)	DTKFHKS (SEQ ID NO: 1317)	DTLFHKS (SEQ ID NO: 1459)
DTSFHRS (SEQ ID NO: 625)	DTFFHRS (SEQ ID NO: 762)	DTYFHRS (SEQ ID NO: 906)	DTRFHRS (SEQ ID NO: 1039)	DTMFHRS (SEQ ID NO: 1174)	DTKFHRS (SEQ ID NO: 1318)	DTLFHRS (SEQ ID NO: 1460)
DTSFHHS (SEQ ID NO: 626)	DTFFHHS (SEQ ID NO: 763)	DTYFHHS (SEQ ID NO: 907)	DTRFHHS (SEQ ID NO: 1040)	DTMFHHS (SEQ ID NO: 1175)	DTKFHHS (SEQ ID NO: 1319)	DTLFHHS (SEQ ID NO: 1461)
DTSFHPS (SEQ ID NO: 627)	DTFFHPS (SEQ ID NO: 764)	DTYFHPS (SEQ ID NO: 908)	DTRFHPS (SEQ ID NO: 1041)	DTMFHPS (SEQ ID NO: 1176)	DTKFHPS (SEQ ID NO: 1320)	DTLFHPS (SEQ ID NO: 1462)
DTSFHTS (SEQ ID NO: 628)	DTFFHTS (SEQ ID NO: 765)	DTYFHTS (SEQ ID NO: 909)	DTRFHTS (SEQ ID NO: 1042)	DTMFHTS (SEQ ID NO: 1177)	DTKFHTS (SEQ ID NO: 1321)	DTLFHTS (SEQ ID NO: 1463)
DTSFHDS (SEQ ID NO: 629)	DTFFHDS (SEQ ID NO: 766)	DTYFHDS (SEQ ID NO: 910)	DTRFHDS (SEQ ID NO: 1043)	DTMFHDS (SEQ ID NO: 1178)	DTKFHDS (SEQ ID NO: 1322)	DTLFHDS (SEQ ID NO: 1464)
DTSFQAS (SEQ ID NO: 630)	DTFFQAS (SEQ ID NO: 767)	DTYFQAS (SEQ ID NO: 911)	DTRFQAS (SEQ ID NO: 1044)	DTMFQAS (SEQ ID NO: 1179)	DTKFQAS (SEQ ID NO: 1323)	DTLFQAS (SEQ ID NO: 1465)
DTSFQSS (SEQ ID NO: 631)	DTFFQSS (SEQ ID NO: 768)	DTYFQSS (SEQ ID NO: 912)	DTRFQSS (SEQ ID NO: 1045)	DTMFQSS (SEQ ID NO: 1180)	DTKFQSS (SEQ ID NO: 1324)	DTLFQSS (SEQ ID NO: 1466)
DTSFQKS (SEQ ID NO: 632)	DTFFQKS (SEQ ID NO: 769)	DTYFQKS (SEQ ID NO: 913)	DTRFQKS (SEQ ID NO: 1046)	DTMFQKS (SEQ ID NO: 1181)	DTKFQKS (SEQ ID NO: 1325)	DTLFQKS (SEQ ID NO: 1467)
DTSFQORS (SEQ ID NO: 633)	DTFFQORS (SEQ ID NO: 770)	DTYFQORS (SEQ ID NO: 914)	DTRFQORS (SEQ ID NO: 1047)	DTMFQORS (SEQ ID NO: 1182)	DTKFQORS (SEQ ID NO: 1326)	DTLFQORS (SEQ ID NO: 1468)

DTSFQHS (SEQ ID NO: 634)	DTFFQHS (SEQ ID NO: 771)	DTYFQHS (SEQ ID NO: 915)	DTRFQHS (SEQ ID NO: 1048)	DTMFQHS (SEQ ID NO: 1183)	DTKFQHS (SEQ ID NO: 1327)	DTLFQHS (SEQ ID NO: 1469)
DTSFQPS (SEQ ID NO: 635)	DTFFQPS (SEQ ID NO: 772)	DTYFQPS (SEQ ID NO: 916)	DTRFQPS (SEQ ID NO: 1049)	DTMFQPS (SEQ ID NO: 1184)	DTKFQPS (SEQ ID NO: 1328)	DTLFQPS (SEQ ID NO: 1470)
DTSFQTS (SEQ ID NO: 636)	DTFFQTS (SEQ ID NO: 773)	DTYFQTS (SEQ ID NO: 917)	DTRFQTS (SEQ ID NO: 1050)	DTMFQTS (SEQ ID NO: 1185)	DTKFQTS (SEQ ID NO: 1329)	DTLFQTS (SEQ ID NO: 1471)
DTSFQDS (SEQ ID NO: 637)	DTFFQDS (SEQ ID NO: 774)	DTYFQDS (SEQ ID NO: 918)	DTRFQDS (SEQ ID NO: 1051)	DTMFQDS (SEQ ID NO: 1186)	DTKFQDS (SEQ ID NO: 1330)	DTLFQDS (SEQ ID NO: 1472)
DTSLLAS (SEQ ID NO: 124)	DTFLLAS (SEQ ID NO: 775)	DTYLLAS (SEQ ID NO: 919)	DTRLAS (SEQ ID NO: 1052)	DTMLLAS (SEQ ID NO: 1187)	DTKLAS (SEQ ID NO: 1331)	DTLLAS (SEQ ID NO: 133)
DTSLLS (SEQ ID NO: 638)	DTFLS (SEQ ID NO: 776)	DTYLLS (SEQ ID NO: 920)	DTRLSS (SEQ ID NO: 1053)	DTMLSS (SEQ ID NO: 1188)	DTKLSS (SEQ ID NO: 1332)	DTLLS (SEQ ID NO: 1473)
DTSLKS (SEQ ID NO: 639)	DTFLKS (SEQ ID NO: 777)	DTYLLKS (SEQ ID NO: 921)	DTRLKS (SEQ ID NO: 1054)	DTMLKS (SEQ ID NO: 1189)	DTKLKS (SEQ ID NO: 1333)	DTLLKS (SEQ ID NO: 1474)
DTSLRS (SEQ ID NO: 640)	DTFLRS (SEQ ID NO: 778)	DTYLLRS (SEQ ID NO: 922)	DTRLRS (SEQ ID NO: 1055)	DTMLRS (SEQ ID NO: 1190)	DTKLRS (SEQ ID NO: 1334)	DTLLRS (SEQ ID NO: 1475)
DTSLHS (SEQ ID NO: 641)	DTFLHS (SEQ ID NO: 779)	DTYLLHS (SEQ ID NO: 923)	DTRLHS (SEQ ID NO: 1056)	DTMLHS (SEQ ID NO: 1191)	DTKLHS (SEQ ID NO: 1335)	DTLLHS (SEQ ID NO: 1476)
DTSLPS (SEQ ID NO: 642)	DTFLPS (SEQ ID NO: 780)	DTYLLPS (SEQ ID NO: 924)	DTRLPS (SEQ ID NO: 1057)	DTMLPS (SEQ ID NO: 1192)	DTKLPS (SEQ ID NO: 1336)	DTLLPS (SEQ ID NO: 1477)
DTSLTS (SEQ ID NO: 643)	DTFLTTS (SEQ ID NO: 781)	DTYLLTS (SEQ ID NO: 925)	DTRLTS (SEQ ID NO: 1058)	DTMLTS (SEQ ID NO: 1193)	DTKLTS (SEQ ID NO: 1337)	DTLLTS (SEQ ID NO: 1478)

DTSLILDS (SEQ ID NO:126)	DTFLILDS (SEQ ID NO:782)	DTYLILDS (SEQ ID NO:926)	DTRLILDS (SEQ ID NO:1059)	DTMLILDS (SEQ ID NO:1194)	DTKLILDS (SEQ ID NO:1338)	DTLLILDS (SEQ ID NO:75)
DTSLHAS (SEQ ID NO:644)	DTFLHAS (SEQ ID NO:783)	DTYLHAS (SEQ ID NO:927)	DTRLHAS (SEQ ID NO:1060)	DTMLHAS (SEQ ID NO:1195)	DTKLHAS (SEQ ID NO:1339)	DTLLHAS (SEQ ID NO:1479)
DTSLHSS (SEQ ID NO:645)	DTFLHSS (SEQ ID NO:784)	DTYLHSS (SEQ ID NO:928)	DTRLHSS (SEQ ID NO:1061)	DTMLHSS (SEQ ID NO:1196)	DTKLHSS (SEQ ID NO:1340)	DTLLHSS (SEQ ID NO:1480)
DTSLHKS (SEQ ID NO:646)	DTFLHKS (SEQ ID NO:785)	DTYLHKS (SEQ ID NO:929)	DTRLHKS (SEQ ID NO:1062)	DTMLHKS (SEQ ID NO:1197)	DTKLHKS (SEQ ID NO:1341)	DTLLHKS (SEQ ID NO:1481)
DTSLHRS (SEQ ID NO:647)	DTFLHRS (SEQ ID NO:786)	DTYLHRS (SEQ ID NO:930)	DTRLHRS (SEQ ID NO:1063)	DTMLHRS (SEQ ID NO:1198)	DTKLHRS (SEQ ID NO:1342)	DTLLHRS (SEQ ID NO:1482)
DTSLHHS (SEQ ID NO:648)	DTFLHHS (SEQ ID NO:787)	DTYLHHS (SEQ ID NO:931)	DTRLHHS (SEQ ID NO:1064)	DTMLHHS (SEQ ID NO:1199)	DTKLHHS (SEQ ID NO:1343)	DTLLHHS (SEQ ID NO:1483)
DTSLHPS (SEQ ID NO:649)	DTFLHPS (SEQ ID NO:788)	DTYLHPS (SEQ ID NO:932)	DTRLHPS (SEQ ID NO:1065)	DTMLHPS (SEQ ID NO:1200)	DTKLHPS (SEQ ID NO:1344)	DTLLHPS (SEQ ID NO:1484)
DTSLHTS (SEQ ID NO:650)	DTFLHTS (SEQ ID NO:789)	DTYLHTS (SEQ ID NO:933)	DTRLHTS (SEQ ID NO:1066)	DTMLHTS (SEQ ID NO:1201)	DTKLHTS (SEQ ID NO:1345)	DTLLHTS (SEQ ID NO:1485)
DTSLHDS (SEQ ID NO:651)	DTFLHDS (SEQ ID NO:790)	DTYLHDS (SEQ ID NO:934)	DTRLHDS (SEQ ID NO:1067)	DTMLHDS (SEQ ID NO:1202)	DTKLHDS (SEQ ID NO:1346)	DTLLHDS (SEQ ID NO:1486)
DTSLQAS (SEQ ID NO:652)	DTFLQAS (SEQ ID NO:791)	DTYLQAS (SEQ ID NO:935)	DTRLQAS (SEQ ID NO:1068)	DTMLQAS (SEQ ID NO:1203)	DTKLQAS (SEQ ID NO:1347)	DTLLQAS (SEQ ID NO:1487)
DTSLQSS (SEQ ID NO:653)	DTFLQSS (SEQ ID NO:792)	DTYLQSS (SEQ ID NO:936)	DTRLQSS (SEQ ID NO:1069)	DTMLQSS (SEQ ID NO:1204)	DTKLQSS (SEQ ID NO:1348)	DTLLQSS (SEQ ID NO:1488)

<u>DTSLQKS</u> (SEQ ID NO: 654)	<u>DTFLQKS</u> (SEQ ID NO: 793)	<u>DTYLQKS</u> (SEQ ID NO: 937)	<u>DTRLQKS</u> (SEQ ID NO: 1070)	<u>DTMLQKS</u> (SEQ ID NO: 1205)	<u>DTKLQKS</u> (SEQ ID NO: 1349)	<u>DTLLQKS</u> (SEQ ID NO: 1489)
<u>DTSLQRS</u> (SEQ ID NO: 655)	<u>DTFLQRS</u> (SEQ ID NO: 794)	<u>DTYLQRS</u> (SEQ ID NO: 938)	<u>DTRLQRS</u> (SEQ ID NO: 1071)	<u>DTMLQRS</u> (SEQ ID NO: 1206)	<u>DTKLQRS</u> (SEQ ID NO: 1350)	<u>DTLLQRS</u> (SEQ ID NO: 1490)
<u>DTSLQHS</u> (SEQ ID NO: 656)	<u>DTFLQHS</u> (SEQ ID NO: 795)	<u>DTYLQHS</u> (SEQ ID NO: 939)	<u>DTRLQHS</u> (SEQ ID NO: 1072)	<u>DTMLQHS</u> (SEQ ID NO: 1207)	<u>DTKLQHS</u> (SEQ ID NO: 1351)	<u>DTLLQHS</u> (SEQ ID NO: 1491)
<u>DTSLQPS</u> (SEQ ID NO: 657)	<u>DTFLQPS</u> (SEQ ID NO: 796)	<u>DTYLQPS</u> (SEQ ID NO: 940)	<u>DTRLQPS</u> (SEQ ID NO: 1073)	<u>DTMLQPS</u> (SEQ ID NO: 1208)	<u>DTKLQPS</u> (SEQ ID NO: 1352)	<u>DTLLQPS</u> (SEQ ID NO: 1492)
<u>DTSLQTS</u> (SEQ ID NO: 658)	<u>DTFLQTS</u> (SEQ ID NO: 797)	<u>DTYLQTS</u> (SEQ ID NO: 941)	<u>DTRLQTS</u> (SEQ ID NO: 1074)	<u>DTMLQTS</u> (SEQ ID NO: 1209)	<u>DTKLQTS</u> (SEQ ID NO: 1353)	<u>DTLLQTS</u> (SEQ ID NO: 1493)
<u>DTSLQDS</u> (SEQ ID NO: 659)	<u>DTFLQDS</u> (SEQ ID NO: 798)	<u>DTYLQDS</u> (SEQ ID NO: 942)	<u>DTRLQDS</u> (SEQ ID NO: 1075)	<u>DTMLQDS</u> (SEQ ID NO: 1210)	<u>DTKLQDS</u> (SEQ ID NO: 1354)	<u>DTLLQDS</u> (SEQ ID NO: 1494)

Bold faced & underlined amino acid residues are the residues which differ from the amino acid sequence in palivizumab

**Table 3F - VL CDR3 Sequences**

EQSGGYPFT (SEQ ID NO: 6)
EQGS <b>F</b> YPFT (SEQ ID NO: 61)
EQGS <b>Y</b> YPFT (SEQ ID NO: 1495)
EQGS <b>W</b> YPFT (SEQ ID NO: 1496)

Bold faced and underlined amino acid residues are the residues which differ from the amino acid sequence in palivizumab

[00182] In one embodiment, formulations of the present invention comprise antibodies that comprise a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18. In another embodiment, formulations of the present invention comprise antibodies that comprise a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:305, or SEQ ID NO:329. In another embodiment, formulations of the present invention comprise antibodies that comprise a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, or SEQ ID NO:311. In another embodiment, formulations of the present invention comprise antibodies that comprise a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18, a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:305, or SEQ ID NO:329, and a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, or SEQ ID NO:311. In a preferred embodiment, formulations of the present invention comprise antibodies that comprise a VH CDR1 having the amino acid sequence of SEQ ID NO:10, a VH CDR2 having the amino acid sequence of SEQ ID NO:19, and a VH CDR3 having the amino acid sequence of SEQ ID NO:20. In accordance with these embodiments, the antibodies immunspecifically bind to a RSV F antigen. In specific embodiments, the antibodies are not palivizumab, a Fab fragment of palivizumab, or an antigen-binding fragment thereof. In specific embodiments, the antibodies have a high affinity for a RSV antigen (*e.g.*, RSV F antigen).

[00183] In one embodiment, the amino acid sequence of the VH domain is

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Q   V   T   L   R   E   S   G   P   A   L   V   K   P   T
Q   T   L   T   L   T   C   T   F   S   G   F   S   L   S
T   A   G   M   S   V   G   W   I   R   Q   P   P   G   K
A   L   E   W   L   A   D   I   W   W   D   D   K   K   H
Y   N   P   S   L   K   D   R   L   T   I   S   K   D   T
S   K   N   Q   V   V   L   K   V   T   N   M   D   P   A
D   T   A   T   Y   Y   C   A   R   D   M   I   F   N   F
Y   F   D   V   W   G   Q*   G   T   T   V   T   V   S   S

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(SEQ ID NO:48), wherein the three underlined regions indicate the VH CDR1, CDR2, and CDR3 regions, respectively; the four non-underlined regions correlate with the VL FR1, FR2, FR3, FR4, respectively; and the asterisk indicates the position of an A→Q mutation in VH FR4

as compared to the VH FR4 of palivizumab shown in Figure 1B(SEQ ID NO:7). This VH domain (SEQ ID NO:48) is identical to that of the motavizumab antibody described elsewhere herein and shown in Figure 13A. In some embodiments, this VH FR can be used in combination with any of the VH CDRs identified in Table 1 and/or Tables 3A-C. In one embodiment, the motavizumab antibody comprises the VH domain of Figure 13A (SEQ ID NO:208) and the C-gamma-1 (nG1m) constant domain described in Johnson et al. (1997) *J. Infect. Dis.* 176, 1215-1224 and U.S. Patent No. 5,824,307. In one embodiment, an antibody of the invention comprises a VH chain having the amino acid sequence of SEQ ID NO:208.

**[00184]** The present invention provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigen), said antibodies comprising a VL chain having an amino acid sequence of any one of the VL chain listed in Table 2. In certain embodiments, the antibody is not palivizumab and/or the VL chain is not the VL chain of palivizumab.

**[00185]** The present invention also provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigens), said antibodies comprising a variable light ("VL") domain having an amino acid sequence of any one of the VL domains listed in Table 2. In certain embodiments, the antibody is not palivizumab and/or the VH domain is not the VH domain of palivizumab. The present invention also provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigens), said antibodies comprising a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 2 and/or Tables 3D-3F. In certain embodiments, the antibody is not palivizumab. In some embodiments, the antibody comprises one, two or three of the VL CDRs listed in Table 2 and/or Tables 3D-3F.

**[00186]** In one embodiment of the present invention, antibodies comprise a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:72, SEQ ID NO:314, SEQ ID NO:320, or SEQ ID NO:335. In another embodiment, formulations of the invention comprise antibodies that comprise a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:308, SEQ ID NO:315, SEQ ID NO:321, SEQ ID NO:326, SEQ ID NO:332, or SEQ ID NO:336. In another embodiment, formulations of the invention comprise antibodies that comprise a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61. In another embodiment, formulations of the invention comprise antibodies that comprise a VL CDR1

having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:72, SEQ ID NO:314, SEQ ID NO:320, or SEQ ID NO:335, a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:308, SEQ ID NO:315, SEQ ID NO:321, SEQ ID NO:326, SEQ ID NO:332, or SEQ ID NO:336, and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61. In a preferred embodiment, formulations of the invention comprise antibodies that comprise a VL CDR1 having the amino acid sequence of SEQ ID NO:39, a VLCDR2 having the amino acid sequence of SEQ ID NO:5, and a VLCDR3 having the amino acid sequence of SEQ ID NO:6. In accordance with these embodiments, the antibodies immunospecifically bind to a RSV F antigen. In specific embodiments, the antibodies are not palivizumab or an antigen-binding fragment thereof (*e.g.*, a Fab fragment of palivizumab). In another specific embodiment, the antibodies have a high affinity for RSV antigen (*e.g.*, RSV F antigen).

**[00187]** In one embodiment the amino acid sequence of the VL domain is

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D   I   Q   M   T   Q   S   P   S   T   L   S   A   S   V
G   D   R   V   T   I   T   C   S   A   S   S   R   V   G
Y   M   H   W   Y   Q   Q   K   P   G   K   A   P   K   L
L   I   Y   D   T   S   K   L   A   S   G   V   P   S   R
F   S   G   S   G   S   G   T   E   F   T   L   T   I   S
S   L   Q   P   D   D   F   A   T   Y   Y   C   F   Q   G
S   G   Y   P   F   T   F   G   G   G   T   K   V*   E   I

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K

(SEQ ID NO:8), wherein the three underlined regions indicate the VL CDR1, CDR2, and CDR3 regions, respectively; the four non-underlined regions correlate with the VL FR1, FR2, FR3, FR4, respectively; and the asterisk indicates the position of an L→V mutation in VL FR4 as compared to the VL FR4 of palivizumab shown in Figure 1A. This VL domain (SEQ ID NO:8) is identical to that of the motavizumab antibody described elsewhere herein and shown in Figure 13B. In some embodiments, this VL framework can be used in combination with any of the VL CDRs identified in Table 1 and/or Tables 3D-3F. In one embodiment, the motavizumab



antibody comprises the VL domain of Figure 13B (SEQ ID NO:209) and the C-kappa constant domain described in Johnson et al. (1997) *J. Infect. Dis.* 176, 1215-1224 and U.S. Patent No. 5,824,307. In one embodiment, an antibody of the invention comprises a VL chain having the amino acid sequence of SEQ ID NO:209.

**[00188]** The present invention further provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigen), wherein the antibody comprises a VH chain disclosed herein combined with a VL chain disclosed herein, or other VL chain. The present invention also provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigen), wherein the antibody comprises a VL chain disclosed herein combined with a VH chain disclosed herein, or other VH chain.

**[00189]** The present invention also provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigens), said antibodies comprising a VH domain disclosed herein combined with a VL domain disclosed herein, or other VL domain. The present invention further provides antibodies that immunospecifically bind to one or more RSV antigens (*e.g.*, RSV F antigens), said antibodies comprising a VL domain disclosed herein combined with a VH domain disclosed herein, or other VH domain.

**[00190]** In a specific embodiment, antibodies that immunospecifically bind to a RSV antigen (*e.g.*, RSV F antigens) comprise a VH domain having the amino acid sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:51, SEQ ID NO:55, SEQ ID NO:67, SEQ ID NO:78, SEQ ID NO:304, SEQ ID NO:310, SEQ ID NO:317, SEQ ID NO:323, or SEQ ID NO:328, and a VL domain having the amino acid sequence of SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:21, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:49, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:307, SEQ ID NO:313, SEQ ID NO:319, SEQ ID NO:325, SEQ ID NO:331, or SEQ ID NO:334. In a preferred embodiment, antibodies that immunospecifically bind to a RSV F antigen comprise a VH domain having the amino acid sequence of SEQ ID NO:48 and a VL domain comprising the amino acid sequence of SEQ ID NO:11. In specific embodiments, the antibodies are not palivizumab or an antigen-binding fragment thereof (*e.g.*, a Fab fragment). In another specific embodiment, the antibodies of the invention have a high affinity for a RSV antigen (*e.g.*, RSV F antigen).

**[00191]** The present invention further provides antibodies that specifically bind to an RSV antigen (*e.g.*, RSV F antigen), wherein the antibody comprises any VH CDR1 disclosed herein, optionally in combination with any VH CDR2 disclosed herein (or other VH CDR2), and/or optionally in combination with any VH CDR3 disclosed herein (or other VH CDR3)), and/or optionally in combination with any VL CDR1 disclosed herein (or other VL CDR1), and/or optionally in combination with any VL CDR2 disclosed herein (or other VL CDR2), and/or optionally in combination with any VL CDR3 disclosed herein (or other VL CDR3). The present invention also provides antibodies that specifically bind to an RSV antigen (*e.g.*, RSV F antigen), wherein the antibody comprises any VH CDR2 disclosed herein, optionally in combination with any VH CDR1 disclosed herein (or other VH CDR1), and/or optionally in combination with any VH CDR3 disclosed herein (or other VH CDR3)), and/or optionally in combination with any VL CDR1 disclosed herein (or other VL CDR1), and/or optionally in combination with any VL CDR2 disclosed herein (or other VL CDR2), and/or optionally in combination with any VL CDR3 disclosed herein (or other VL CDR3). The present invention also provides antibodies that specifically bind to an RSV antigen (*e.g.*, RSV F antigen), wherein the antibody comprises any VH CDR3 disclosed herein, optionally in combination with any VH CDR1 disclosed herein (or other VH CDR1), and/or optionally in combination with any VH CDR2 disclosed herein (or other VH CDR2)), and/or optionally in combination with any VL CDR1 disclosed herein (or other VL CDR1), and/or optionally in combination with any VL CDR2 disclosed herein (or other VL CDR2), and/or optionally in combination with any VL CDR3 disclosed herein (or other VL CDR3). The present invention also provides antibodies that specifically bind to an RSV antigen (*e.g.*, RSV F antigen), wherein the antibody comprises any VL CDR1 disclosed herein, optionally in combination with any VH CDR1 disclosed herein (or other VH CDR1), and/or optionally in combination with any VH CDR2 disclosed herein (or other VH CDR2)), and/or optionally in combination with any VH CDR3 disclosed herein (or other VH CDR3), and/or optionally in combination with any VL CDR2 disclosed herein (or other VL CDR2), and/or optionally in combination with any VL CDR3 disclosed herein (or other VL CDR3). The present invention further provides antibodies that specifically bind to an RSV antigen (*e.g.*, RSV F antigen), wherein the antibody comprises any VL CDR2 disclosed herein, optionally in combination with any VH CDR1 disclosed herein (or other VH CDR1), and/or optionally in combination with any VH CDR2 disclosed herein (or other VH CDR2)), and/or optionally in combination with any VH CDR3 disclosed herein (or other VH CDR3), and/or optionally in combination with any VL CDR1 disclosed herein (or other VL CDR1), and/or optionally in combination with any VL CDR3 disclosed herein (or other VL CDR3). The present invention also provides antibodies that specifically bind to an RSV antigen (*e.g.*, RSV F

antigen), wherein the antibody comprises any VL CDR3 disclosed herein, optionally in combination with any VH CDR1 disclosed herein (or other VH CDR1), and/or optionally in combination with any VH CDR2 disclosed herein (or other VH CDR2)), and/or optionally in combination with any VH CDR3 disclosed herein (or other VH CDR3), and/or optionally in combination with any VL CDR1 disclosed herein (or other VL CDR1), and/or optionally in combination with any VL CDR2 disclosed herein (or other VL CDR2).

**[00192]** The present invention also provides antibodies comprising one or more VH CDRs and one or more VL CDRs listed in Table 2 and/or Tables 3A-3F. In particular, the invention provides for an antibody comprising a VH CDR1 and a VL CDR1; a VH CDR1 and a VL CDR2; a VH CDR1 and a VL CDR3; a VH CDR2 and a VL CDR1; VH CDR2 and VL CDR2; a VH CDR2 and a VL CDR3; a VH CDR3 and a VH CDR1; a VH CDR3 and a VL CDR2; a VH CDR3 and a VL CDR3; a VH1 CDR1, a VH CDR2 and a VL CDR1; a VH CDR1, a VH CDR2 and a VL CDR2; a VH CDR1, a VH CDR2 and a VL CDR3; a VH CDR2, a VH CDR3 and a VL CDR1, a VH CDR2, a VH CDR3 and a VL CDR2; a VH CDR2, a VH CDR2 and a VL CDR3; a VH CDR1, a VL CDR1 and a VL CDR2; a VH CDR1, a VL CDR1 and a VL CDR3; a VH CDR2, a VL CDR1 and a VL CDR2; a VH CDR2, a VL CDR1 and a VL CDR3; a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR1, a VH CDR2, a VH CDR3 and a VL CDR1; a VH CDR1, a VH CDR2, a VH CDR3 and a VL CDR2; a VH CDR1, a VH CDR2, a VH CDR3 and a VL CDR3; a VH CDR1, a VH CDR2, a VL CDR1 and a VL CDR2; a VH CDR1, a VH CDR2, a VL CDR1 and a VL CDR3; a VH CDR1, a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR1, a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR2, a VH CDR3, a VL CDR2 and a VL CDR3; a VH CDR1, a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR1, a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR1, a VH CDR2, a VL CDR1, a VL CDR2, and a VL CDR3; a VH CDR1, a VH CDR3, a VL CDR1, a VL CDR2, and a VL CDR3; a VH CDR2, a VH CDR3, a VL CDR1, a VL CDR2, and a VL CDR3; or any combination thereof of the VH CDRs and VL CDRs listed in Table 2 and/or Tables 3A-3F. In a specific embodiment, the formulations of the invention comprise antibodies that have a high affinity for a RSV antigen (*e.g.*, RSV F antigen).

**[00193]** The invention also provides an antibody that immunospecifically binds to a RSV F antigen, comprising a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR1 and a VL CDR1; a VH CDR1 and a VL CDR2; a VH CDR1 and

a VL CDR3; a VH CDR2 and a VL CDR1; VH CDR2 and VL CDR2; a VH CDR2 and a VL CDR3; a VH CDR3 and a VH CDR1; a VH CDR3 and a VL CDR2; a VH CDR3 and a VL CDR3; a VH1 CDR1, a VH CDR2 and a VL CDR1; a VH CDR1, a VH CDR2 and a VL CDR2; a VH CDR1, a VH CDR2 and a VL CDR3; a VH CDR2, a VH CDR3 and a VL CDR1, a VH CDR2, a VH CDR3 and a VL CDR2; a VH CDR2, a VH CDR2 and a VL CDR3; a VH CDR1, a VL CDR1 and a VL CDR2; a VH CDR1, a VL CDR1 and a VL CDR3; a VH CDR2, a VL CDR1 and a VL CDR2; a VH CDR2, a VL CDR1 and a VL CDR3; a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR1, a VH CDR2, a VH CDR3 and a VL CDR1; a VH CDR1, a VH CDR2, a VH CDR3 and a VL CDR2; a VH CDR1, a VH CDR2, a VH CDR3 and a VL CDR3; a VH CDR1, a VH CDR2, a VL CDR1 and a VL CDR2; a VH CDR1, a VH CDR2, a VL CDR1 and a VL CDR3; a VH CDR1, a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR1, a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR2, a VH CDR3, a VL CDR2 and a VL CDR3; a VH CDR1, a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR2; a VH CDR1, a VH CDR2, a VH CDR3, a VL CDR1 and a VL CDR3; a VH CDR1, a VH CDR2, a VL CDR1, a VL CDR2, and a VL CDR3; a VH CDR1, a VH CDR3, a VL CDR1, a VL CDR2, and a VL CDR3; a VH CDR2, a VH CDR3, a VL CDR1, a VL CDR2, and a VL CDR3; or any combination thereof of the VH CDRs and VL CDRs listed in Table 2 and/or Tables 3A-3F, *supra*. In another specific embodiment, the formulations of the invention comprise antibodies that have a high affinity for a RSV antigen (*e.g.*, RSV F antigen).

**[00194]** In one embodiment, a formulation of the invention comprises an antibody that comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18 and a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:314, SEQ ID NO:320, or SEQ ID NO:335. In another embodiment, a formulation of the invention comprises an antibody that comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or SEQ ID NO:18 and a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:308, SEQ ID NO:315, SEQ ID NO:321, SEQ ID NO:326, SEQ ID NO:332, or SEQ ID NO:336. In another embodiment, a formulation of the invention comprises an antibody that comprises a VH CDR1 having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:10 or

SEQ ID NO:18 and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16 or SEQ ID NO:61. In accordance with these embodiments, the antibody immunospecifically binds to a RSV F antigen.

**[00195]** In another embodiment, a formulation of the invention comprises an antibody that comprises a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:305, or SEQ ID NO:329, and a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:314, SEQ ID NO:320, or SEQ ID NO:335. In another embodiment, an antibody of the invention comprises a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:305, or SEQ ID NO:329, and a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:308, SEQ ID NO:315, SEQ ID NO:321, SEQ ID NO:326, SEQ ID NO:332, or SEQ ID NO:336. In another embodiment, an antibody of the invention comprises a VH CDR2 having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:37, SEQ ID NO:41, SEQ ID NO:45, SEQ ID NO:305, or SEQ ID NO:329, and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61. In accordance with these embodiments, the antibody immunospecifically binds to a RSV F antigen.

**[00196]** In another embodiment, a formulation of the invention comprises an antibody that comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, or SEQ ID NO:311, and a VL CDR1 having the amino acid sequence of SEQ ID NO:4, SEQ ID NO:14, SEQ ID NO:22, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:314, SEQ ID NO:320, or SEQ ID NO:335. In another embodiment, a formulation of the invention comprises an antibody that comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, or SEQ ID NO:311, and a VL CDR2 having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:27, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:50, SEQ ID NO:53, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:308, SEQ ID NO:315, SEQ ID NO:321, SEQ ID NO:326, SEQ ID

NO:332, or SEQ ID NO:336. In a preferred embodiment, an antibody of the invention comprises a VH CDR3 having the amino acid sequence of SEQ ID NO:3, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:29, SEQ ID NO:79, or SEQ ID NO:311, and a VL CDR3 having the amino acid sequence of SEQ ID NO:6, SEQ ID NO:16, or SEQ ID NO:61. In accordance with these embodiments, the antibody immunospecifically binds to a RSV F antigen.

**[00197]** The present invention provides antibodies that immunospecifically bind to a RSV F antigen, said antibodies comprising the amino acid sequence of the variable heavy domain and/or variable light domain or an antigen-binding fragment thereof of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4 with one or more amino acid residue substitutions in the variable heavy domain and/or variable light domain or antigen-binding fragment. The present invention also provides antibodies that immunospecifically bind to a RSV antigen, said antibodies comprising the amino acid sequence of the variable heavy domain and/or variable light domain or an antigen-binding fragment thereof of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4 with one or more amino acid residue substitutions in one or more VH CDRs and/or one or more VL CDRs. Non-limiting examples of amino acid residues in the VH CDRs and VL CDRs of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4, which may be substituted, are shown in bold in Table 2. The present invention also provides antibodies that immunospecifically bind to a RSV antigen, said antibodies comprising the amino acid sequence of the variable heavy domain and/or variable light domain or an antigen-binding fragment thereof of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4 with one or more amino acid residue substitutions in one or more VH frameworks and/or one or more VL frameworks. The antibody generated by introducing substitutions in the VH domain, VH CDRs, VL domain, VL CDRs and/or frameworks of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-

S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4 can be tested *in vitro* and/or *in vivo*, for example, for its ability to bind to a RSV antigen, or for its ability to prevent, treat and/or ameliorate a an upper and/or lower respiratory tract RSV infection, otitis media, or one or more symptoms thereof.

**[00198]** In a specific embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence encoded by a nucleotide sequence that hybridizes to the nucleotide sequence(s) encoding palivizumab, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (MEDI-524, motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, A17h4, or an antigen-binding fragment thereof under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3).

**[00199]** In another embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4, or an antigen-binding fragment thereof. In preferred embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to an amino acid sequence of A4B4L1FR-S28R (motavizumab), or an antigen-binding fragment thereof.

**[00200]** In a specific embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence of a VH domain and/or an amino acid sequence a VL

domain encoded by a nucleotide sequence that hybridizes to the nucleotide sequence encoding any one of the VH and/or VL domains listed in Table 2 under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody that immunospecifically binds to a RSV antigen comprises an amino acid sequence of a VH CDR or an amino acid sequence of a VL CDRs encoded by a nucleotide sequence that hybridizes to the nucleotide sequence encoding any one of the VH CDRs or VL CDRs listed in Table 2 and/or Tables 3A-3F under stringent conditions *e.g.*, hybridization to filter-bound DNA in 6X sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6X SSC at about 45° C followed by one or more washes in 0.1X SSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art. In yet another embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence of a VH CDR and an amino acid sequence of a VL CDR encoded by nucleotide sequences that hybridizes to the nucleotide sequences encoding any one of the VH CDRs and VL CDRs, respectively, listed in Table 2 and/or Tables 3A-3F under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6X sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6X SSC at about 45° C followed by one or more washes in 0.1X SSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art.

**[00201]** In another embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence of a VH domain that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH domains listed in Table 2. In another embodiment, an antibody that immunospecifically binds to a RSV antigen comprises an amino acid sequence of one or more VH CDRs that are at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at



least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any of the VH CDRs listed in Table 2 and/or Tables 3A-3C. In another embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence of a VL domain that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VL domains listed in Table 2. In another embodiment, an antibody that immunospecifically binds to a RSV F antigen comprises an amino acid sequence of one or more VL CDRs that are at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any of the VL CDRs listed in Table 2 and/or Tables 3D-3F.

**[00202]** The present invention also provides antibodies that compete with an antibody or Fab fragment listed in Table 2 for binding to a RSV F antigen. The present invention also encompasses polypeptides, proteins and peptides comprising VL domains and/or VH domains that compete with a polypeptide, protein or peptide comprising a VL domain and/or a VH domain listed in Table 2 for binding to a RSV F antigen. Further, the present invention encompasses polypeptides, proteins and peptides comprising VL CDRs and/or VH CDRs that compete with a polypeptide, protein or peptide comprising a VL CDR and/or VH CDR listed in Table 2 and/or Tables 3A-3F for binding to a RSV F antigen.

**[00203]** The formulations of the present invention comprise antibodies that include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

**[00204]** The present invention also provides antibodies that immunospecifically bind to a RSV antigen (*e.g.*, RSV F antigen) which comprise a framework region known to those of skill in the art (*e.g.*, a human or non-human fragment). The framework region may be naturally occurring or consensus framework regions. Preferably, the framework region of an antibody of the invention is human (see, *e.g.*, Chothia et al., 1998, J. Mol. Biol. 278:457-479 for a listing of

human framework regions, which is incorporated by reference herein in its entirety). In a specific embodiment, an antibody of the invention comprises the framework region of A4B4L1FR-S28R (motavizumab).

**[00205]** In a specific embodiment, the present invention provides antibodies that immunospecifically bind to a RSV F antigen, said antibodies comprising the amino acid sequence of one or more of the CDRs of an antibody listed in Table 2 (*i.e.*, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4) and/or one or more of the CDRs in Table 3A-3F, and human framework regions with one or more amino acid substitutions at one, two, three or more of the following residues: (a) rare framework residues that differ between the murine antibody framework (*i.e.*, donor antibody framework) and the human antibody framework (*i.e.*, acceptor antibody framework); (b) Venier zone residues when differing between donor antibody framework and acceptor antibody framework; (c) interchain packing residues at the VH/VL interface that differ between the donor antibody framework and the acceptor antibody framework; (d) canonical residues which differ between the donor antibody framework and the acceptor antibody framework sequences, particularly the framework regions crucial for the definition of the canonical class of the murine antibody CDR loops; (e) residues that are adjacent to a CDR; (g) residues capable of interacting with the antigen; (h) residues capable of interacting with the CDR; and (i) contact residues between the VH domain and the VL domain.

**[00206]** The present invention encompasses formulations that comprise antibodies that immunospecifically bind to a RSV F antigen, said antibodies comprising the amino acid sequence of the variable heavy domain and/or variable light domain or an antigen-binding fragment thereof of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4 with mutations (*e.g.*, one or more amino acid substitutions) in the framework regions. In certain embodiments, antibodies that immunospecifically bind to a RSV antigen comprise the amino acid sequence of the variable heavy domain and/or variable light domain or an antigen-binding fragment thereof of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S,

A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4 with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains.

**[00207]** The present invention also encompasses formulations that comprise antibodies which immunospecifically bind to one or more RSV F antigens, said antibodies comprising the amino acid sequence of A4B4L1FR-S28R (motavizumab) with mutations (*e.g.*, one or more amino acid substitutions) in the framework regions. In certain embodiments, antibodies which immunospecifically bind to one or more RSV F antigens comprise the amino acid sequence of A4B4L1FR-S28R (motavizumab) with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains. In a specific embodiment, antibodies which immunospecifically bind to one or more RSV F antigens comprise the framework regions depicted in Figure 2 or Figure 13.

**[00208]** The present invention also provides antibodies that immunospecifically bind to a RSV antigen, said antibodies comprising the amino acid sequence of the variable heavy domain and/or variable light domain of an antibody in Table 2 (*i.e.*, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4) with mutations (*e.g.*, one or more amino acid residue substitutions) in the hypervariable and framework regions. Preferably, the amino acid substitutions in the hypervariable and framework regions improve binding of the antibody to a RSV antigen.

**[00209]** The present invention also provides antibodies which immunospecifically bind to one or more RSV F antigens, said antibodies comprising the amino acid sequence of A4B4L1FR-S28R (motavizumab) with mutations (*e.g.*, one or more amino acid residue substitutions) in the variable and framework regions.

**[00210]** The present invention also provides antibodies that immunospecifically bind to a RSV antigen (*e.g.*, RSV F antigen) which comprise constant regions known to those of skill in the art. Preferably, the constant regions of an antibody of the invention are human. In a specific embodiment, an antibody of the invention comprises the constant regions of A4B4L1FR-S28R (motavizumab).

**[00211]** The present invention also provides fusion proteins comprising an antibody that immunospecifically binds to a RSV antigen and a heterologous polypeptide. Preferably, the

heterologous polypeptide that the antibody is fused to is useful for targeting the antibody to respiratory epithelial cells.

**[00212]** The present invention also encompasses formulations that comprise panels of antibodies that immunospecifically bind to a RSV antigen. In specific embodiments, the invention provides panels of antibodies having different association rate constants different dissociation rate constants, different affinities for a RSV antigen, and/or different specificities for a RSV antigen. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000 antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

**[00213]** The present invention further provides one or more antibodies for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). In a specific embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and/or A17h4. In another specific embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises an antigen-binding fragment of AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), or A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4.

**[00214]** In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma,

wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains listed in Table 2. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 and/or Table 3A. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 and/or Table 3B. In a preferred embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 and/or Table 3C.

**[00215]** In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VL domains having an amino acid sequence of any one of the VL domains listed in Table 2. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 or Table 3D. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 and/or Table 3E. In a preferred embodiment, a formulation for use in the prevention, treatment,

and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 and/or Table 3F.

**[00216]** In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains listed in Table 2 and one or more VL domains having an amino acid sequence of any one of the VL domains listed in Table 2. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 and/or Table 3A and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 and/or Table 3D. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 and/or Table 3A and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 and/or Table 3E. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s listed in Table 2 and/or Table 3A and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 and/or Table 3F.

**[00217]** In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a

symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 and/or Table 3B and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 and/or Table 3D. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 and/or Table 3B and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 and/or Table 3E. In another embodiment, a formulation of the present invention comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s listed in Table 2 and/or Table 3B and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 and/or Table 3F.

**[00218]** In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 and/or Table 3C and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s listed in Table 2 and/or Table 3D. In another embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 and/or Table 3C and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s listed in Table 2 and/or Table 3E. In a preferred embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s listed in Table 2 and/or Table 3C and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s listed in Table 2 and/or

Table 3F. In a preferred embodiment, a formulation for use in the prevention, treatment, and/or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprises A4B4L1FR-S28R (motavizumab) or an antigen-binding fragment thereof. In yet another embodiment, a formulation of the present invention comprises one or more fusion proteins of the invention.

**[00219]** As discussed in more detail below, a formulation of the invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N – or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionucleotides, or toxins. See, *e.g.*, PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

**[00220]** Antibodies of the present invention may be used, for example, to purify, detect, and target RSV antigens, in both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the RSV in biological samples such as sputum. See, *e.g.*, Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

**[00221]** The invention provides an antibody comprising a Fab fragment, which immunospecifically binds to an RSV antigen (*e.g.*, the F protein epitope NSELLSLINDMPITNDQKKLMSNN (SEQ ID NO: 337)), wherein the *T<sub>m</sub>* of the Fab fragment is at least about 87 °C, and wherein said antibody is not any one of palivizumab, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and A17h4. In a specific embodiment, the Fab in such an antibody is different from the Fab of palivizumab. In another embodiment, such an antibody comprises a VH or VL domain that is different from the VH or VL domain of palivizumab. In preferred embodiment, the *T<sub>m</sub>* of the Fab fragment is at least about 90 °C or at least about 93 °C. In another preferred embodiment, the pI of the antibody is between about 8.5 to 9.5 or between about 9.0 to 9.5.



[00222] In another specific embodiment, the antibody comprises a VH domain of the antibody A4B4L1FR-S28R (SEQ ID NO:48). In still another embodiment, the antibody comprises a VL domain of the antibody A4B4L1FR-S28R (SEQ ID NO:11). In still another embodiment, the Fab of the antibody is the Fab of antibody A4B4L1FR-S28R, preferably having one or more amino acid modifications in this constant domain.

[00223] The invention also provides an antibody formulation comprising the above described antibody, said formulation having a viscosity of less than 10.00 cP or less than 5.00cP at any temperature in the range of 1 to 26 °C, or in the range of 5 to 25 °C, or in the range of 10 to 25 °C.

[00224] The invention also provides an antibody formulation comprising the above described antibody, said formulation having an aggregation rate of less than about 5%, 10%, or 15% per day at any temperature in the range of 38 to 42 °C.

[00225] The above described antibodies can be generated by a method described in U.S. Provisional Patent Application No.: 60/696,113, by Christian B. Allan, filed on July 1, 2005, which is incorporated by reference herein in its entirety. In a specific embodiment, such an antibody is generated by a method comprising screening a plurality of candidate antibody domains (*e.g.*, Fab, Fc and Fv) that have high binding affinity to a target (*e.g.*, RSV antigen) for their solubility and thermal stability. Any method known in the art for screening protein domains for their solubility and thermal stability can be used. One or more antibody domains having high solubility and/or thermal stability are then selected and used for constructing the full antibodies by combining them with the appropriate domain(s) to generate a full antibody. In one embodiment, one or more candidate Fab domains that have a T<sub>m</sub> value higher than at least 87°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C, or 120°C are selected for construction of the full antibody. In another embodiment, one or more candidate domains that have a pI value higher than about 6.5, 7.0, 7.5, 8.0, 8.5 or 9.0 are selected for construction of the full antibody. In a specific embodiment, the plurality of candidate Fab domains comprises Fab domains containing one or more amino acid residue substitutions to the Fab domain of the following antibodies palivizumab, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and/or A17h4.

**[00226]** A plurality of antigen binding domains (*e.g.*, Fab, scFv, etc.) that bind a RSV antigen with an affinity above a chosen threshold may be obtained, *e.g.*, by affinity screening of a phage display library. One or more metrics characterizing the antigen binding domains' formulation properties are then evaluated for each of the antigen binding domains. The plurality of antigen binding domains are ranked according to the one or more metrics. In one embodiment, the plurality of antigen binding domains are ranked according to their  $T_m$  values, and one or more antigen binding domains are selected from the top of the ranked list. In another embodiment, the plurality of antigen binding domains are ranked according to their pI values, and one or more antigen binding domains are selected from the top of the ranked list. In still another embodiment, the plurality of antigen binding domains are ranked according to a combined  $T_m$  and pI rank, and one or more antigen binding domains are selected from the top of the ranked list. The selected antigen binding domains are then used for construction of the full anti-RSV antibody molecule (*e.g.*, antibodies, diabodies, etc.).

**[00227]** In another embodiment, a plurality of antibody constant region domains (*e.g.*, Fc, CH2, CH3, etc) is screened for solubility and thermal stability. In one embodiment, one or more candidate antibody constant region domains that have a  $T_m$  value higher than at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C, or 120°C are selected for construction of the full antibody. In another embodiment, one or more candidate antibody constant region domains that have a pI value higher than about 6.5, 7.0, 7.5, 8.0, 8.5 or 9.0 are selected for construction of the full antibody (*e.g.*, antibody, Fc-fusion protein, etc.).

**[00228]** Such an antibody can also be generated by a method for engineering a protein for preferred formulation characteristics and/or properties including but not limited to,  $T_m$ , pI, solubility, stability. In one embodiment, the method comprises engineering one or more domains to improve the antibody's formulation characteristics. In a preferred embodiment, the engineered domain exhibits improved formulation characteristics without reducing significantly the antibody's pharmacological characteristics including but not limited to, the antibody's binding specificity, binding affinity and/or avidity to its target, or the antibody's Fc effector functions, *e.g.*, Fc-receptor (FcR) binding, antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and/or serum half life. In a more preferred embodiment, the engineered domain exhibits improved formulation characteristics without substantially affecting the antibody's pharmacological characteristics.

**[00229]** In a preferred embodiment, a domain is engineered by substituting one or more amino acid residues in the domain such that the stability of the domain is increased. In one embodiment, a domain is engineered such that its  $T_m$  value is increased. In one embodiment, a domain is engineered such that it has a  $T_m$  greater than a predetermined threshold value. In some preferred embodiments, the predetermined  $T_m$  threshold value is at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C, or 120°C. In a specific embodiment, such an engineered Fab domain is generated by substituting one or more amino acid residues in the Fab domain of palivizumab, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, or A17h4.

**[00230]** In another preferred embodiment, a domain is engineered by substituting one or more amino acid residues in the domain such that the solubility of the domain is increased. In one embodiment, a domain is engineered such that its pI value is increased. In one embodiment, a domain is engineered such that it has a pI greater than a predetermined threshold value. In some preferred embodiments, the predetermined pI threshold value is about 6.5, 7.0, 7.5, 8.0, 8.5, or 9.0.

**[00231]** In one embodiment, the antigen binding (*e.g.*, Fab) and/or constant region (*e.g.*, Fc) domains are engineered to improve the protein's formulation characteristics, *e.g.*,  $T_m$ , pI, or stability. In preferred embodiments, the engineered antibody exhibits improved formulation characteristics without reducing significantly the antibody's pharmacological characteristics, *e.g.*, the antibody's binding specificity, binding affinity and/or avidity to its target, or the antibody's Fc effector functions, *e.g.*, Fc-receptor (FcR) binding, antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and/or serum half life. In another embodiment, the engineered antibody exhibits improved formulation characteristics and improved pharmacological characteristics, *e.g.*, the antibody's binding specificity, binding affinity and/or avidity to its target, or the antibody's Fc effector functions, *e.g.*, FcR binding, ADCC, CDC, and/or serum half life.

**[00232]** The solubility of a protein may be optimized by altering the number and location of ionizable residues in the protein to adjust the pI. For example the pI of a polypeptide can be manipulated by making the appropriate amino acid substitutions (*e.g.*, by substituting a charged amino acid such as a lysine, for an uncharged residue such as alanine). Without wishing to be bound by any particular theory, amino acid substitutions of a protein that result in changes of the

pI of said protein may improve solubility and/or the stability of the protein. One skilled in the art would be able to determine amino acid substitutions that is most appropriate for a particular protein to achieve a desired pI. The pI of a protein may be determined by a variety of methods including but not limited to isoelectric focusing. It can also be estimated using any one of the various computer algorithms (see for example Bjellqvist *et al.*, 1993, *Electrophoresis* 14:1023, which is incorporated herein by reference in its entirety).

**[00233]** In one embodiment, the pI of an engineered antibody binding domain is between pH 6.2 and pH 10.0. In one embodiment, substitutions resulting in alterations in the pI of the antigen binding domain will not significantly diminish its binding affinity for an antigen. In one embodiment, the pI of an engineered antibody constant region domain is between pH 6.2 and pH 10.0. In still another embodiment, substitutions resulting in alterations in the pI of the constant region domain will not significantly diminish its effector binding and/or function. It is also contemplated that substitutions resulting in alterations in the pI in an antibody domain may be selected such that both the pI and other pharmacological characteristics of the antibody domain, *e.g.*, the antibody's binding specificity, binding affinity and/or avidity to its target, or the antibody's Fc effector functions are improved. The inventors have found that certain modifications of the hinge region do not change the pI and T<sub>m</sub> of the antibody significantly. Thus, in one embodiment, the invention provides a method for engineering an antibody to improve the antibody's biological activity without reducing the antibody's formulation properties.

**[00234]** In one embodiment, the modifications of an antibody domain as described herein may be combined with known modifications of the Fc domain such as those disclosed in Duncan *et al.*, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J. Immunol* 147:2657-2662; Lund *et al.*, 1992, *Mol Immunol* 29:53-59; Alegre *et al.*, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl. Acad Sci U S A* 92:11980-11984; Jefferis *et al.*, 1995, *Immunol Lett.* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis *et al.*, 1996, *Immunol Lett* 54:101-104; Lund *et al.*, 1996, *Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Idusogie *et al.*, 2000, *J Immunol* 164:4178-4184; Reddy *et al.*, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Idusogie *et al.*, 2001, *J Immunol* 166:2571-2575; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490); U.S. Pat. Nos. 5,624,821; 5,885,573; 6,194,551; U.S. Patent Application Nos. 60/601,634 and 60/608,852; PCT Publication Nos. WO 00/42072 and WO 99/58572; each of which is incorporated herein by reference in its entirety.

**[00235]** In one embodiment, the antibodies may be engineered to include modifications in the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity, without reducing the antibodies' pI and Tm. Furthermore, an antibody may be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody.

**[00236]** In one embodiment, the amino acid sequence of the Fc region is modified by deleting, adding and/or substituting at least amino acid residue to alter one or more of the functional properties of the antibody described above. This approach is described further in Duncan et al, 1988, *Nature* 332:563-564; Lund et al., 1991, *J. Immunol* 147:2657-2662; Lund et al, 1992, *Mol Immunol* 29:53-59; Alegre et al, 1994, *Transplantation* 57:1537-1543; Hutchins et al., 1995, *Proc Natl. Acad Sci U S A* 92:11980-11984; Jefferis et al, 1995, *Immunol Lett.* 44:111-117; Lund et al., 1995, *Faseb J* 9:115-119; Jefferis et al, 1996, *Immunol Lett* 54:101-104; Lund et al, 1996, *J Immunol* 157:4963-4969; Armour et al., 1999, *Eur J Immunol* 29:2613-2624; Idusogie et al, 2000, *J Immunol* 164:4178-4184; Reddy et al, 2000, *J Immunol* 164:1925-1933; Xu et al., 2000, *Cell Immunol* 200:16-26; Idusogie et al, 2001, *J Immunol* 166:2571-2575; Shields et al., 2001, *J Biol Chem* 276:6591-6604; Jefferis et al, 2002, *Immunol Lett* 82:57-65; Presta et al., 2002, *Biochem Soc Trans* 30:487-490); U.S. Patent Nos. 5,624,821; 5,885,573; 5,677,425; 6,165,745; 6,277,375; 5,869,046; 6,121,022; 5,624,821; 5,648,260; 6,194,551; 6,737,056 U.S. Patent Application Nos. 10/370,749 and PCT Publications WO 94/2935; WO 99/58572; WO 00/42072; WO 04/029207, each of which is incorporated herein by reference in its entirety.

**[00237]** In still another embodiment, the glycosylation of antibodies is modified. For example, an aglycosylated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for a target antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Patent Nos. 5,714,350 and 6,350,861, each of which is incorporated herein by reference in its entirety.

**[00238]** Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. See, for example, Shields, R.L. *et al.* (2002) *J. Biol. Chem.* 277:26733-26740; Umana *et al.* (1999) *Nat. Biotech.* 17:176-1, as well as, European Patent No: EP 1,176,195; PCT Publications WO 03/035835; WO 99/54342, each of which is incorporated herein by reference in its entirety.

**[00239]** In another embodiment, the antibodies may be engineered to include modifications in the antigen binding domain to alter the formulation characteristics of the antibody, without reducing the binding characteristics. One skilled in the art will understand that amino acid substitutions and other modifications of an antibody may alter its antigen binding characteristics (examples of binding characteristics include but are not limited to, binding specificity, equilibrium dissociation constant ( $K_D$ ), dissociation and association rates ( $K_{off}$  and  $K_{on}$  respectively), binding affinity and/or avidity) and that certain alterations are more or less desirable. For example a modification that preserves or enhances antigen binding would be more preferable than one that diminished or altered antigen binding. The binding characteristics of an antibody for a target antigen, may be determined by a variety of methods including but not limited to, equilibrium methods (*e.g.*, enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (*e.g.*, BIACORE® analysis; see Example 2), for example. Other commonly used methods to examine the binding characteristics of antibodies are described in *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY, Harrow *et al.*, 1999 and *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY; Harlow *et al.*, 1989.

**[00240]** It is well known in the art that the equilibrium dissociation constant ( $K_D$ ) is defined as  $k_{off}/k_{on}$ . It is generally understood that an antibody with a low  $K_D$  is preferable to an antibody with a high  $K_D$ . However, in some instances the value of the  $k_{on}$  or  $k_{off}$  may be more relevant than the value of the  $K_D$ . One skilled in the art can determine which kinetic parameter is most important for a given antigen binding domain and application. In a preferred embodiment, the method of the invention will result in antigen binding domains with improved

formulation characteristics and one or more antigen binding characteristics (*e.g.*, binding specificity,  $K_D$ ,  $K_{off}$ ,  $K_{on}$ , binding affinity and/or avidity) that are improved by at least 2%, or by at least 5%, or by at least 10%, or by at least 20 %, or by at least 30%, or by at least 40%, or by at least 50%, or by at least 60%, or by at least 70%, or by at least 80% when compared to kinetic parameters of the antigen binding domain without said modification.

[00241] In another embodiment, the method of the invention will result in modified antigen binding domains that have improved formulation characteristics, but do not have substantially diminished antigen binding. For example, the method of the invention will generate antigen binding domains that exhibit improved formulation characteristics, but preferably have no reduction in any antigen binding characteristic (*e.g.*, binding specificity,  $K_D$ ,  $K_{off}$ ,  $K_{on}$ , binding affinity and/or avidity), or have one or more antigen binding characteristics that are reduced by less than 1%, or by less than 5%, or by less than 10%, or by less than 20 %, or by less than 30%, or by less than 40%, or by less than 50%, or by less than 60%, or by less than 70%, or by less than 80% when compared to antigen binding of the antibody without said substitution.

[00242] In one embodiment, selected or engineered antigen binding and antibody constant domains are then used to construct a full anti-RSV antibody using methods known in the art. Such antibodies can then be submitted to formulation development to determine the optimal formulations.

#### **5.3.4 Antibodies that Immunospecifically Bind to Human Metapneumovirus (hMPV)**

[00243] The formulations of the present invention comprise an isolated antibody that specifically binds to an antigen of human metapneumovirus (hMPV) and compositions comprising this antibody. The term “anti-hMPV-antigen antibody” refers to an antibody or antibody fragment thereof that binds immunospecifically to a hMPV antigen. A hMPV antigen refers to a hMPV polypeptide or fragment thereof such as of hMPV nucleoprotein, hMPV phosphoprotein, hMPV matrix protein, hMPV small hydrophobic protein, hMPV RNA-dependent hMPV polymerase, hMPV F protein, and hMPV G protein. A hMPV antigen also refers to a polypeptide that has a similar amino acid sequence compared to a hMPV polypeptide or fragment thereof such as of hMPV nucleoprotein, hMPV phosphoprotein, hMPV matrix protein, hMPV small hydrophobic protein, hMPV RNA-dependent hMPV polymerase, hMPV F protein, and hMPV G protein.

[00244] The anti-hMPV-antigen antibodies used in this invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. In some preferred embodiments, the anti-hMPV antibody of the invention is the antibody disclosed in U.S. Patent Application No. 10/628,088, filed July 25, 2003 and published May 20, 2004, as U.S. Pat. Pub. No. US 2004/0096451 A1.

[00245] The anti-hMPV-antigen antibodies of this section can be made, formulated, administered, used therapeutically or used prophylactically as described in U.S. Patent Application No. 10/628,088, filed July 25, 2003 and published May 20, 2004, as U.S. Pat. Pub. No. US 2004/0096451 A1, the contents of which are hereby incorporated by reference in their entirety.

### **5.3.5 Antibodies that Immunospecifically Bind to Integrin $\alpha_v\beta_3$**

[00246] The formulations of the present invention also comprise an isolated antibody that specifically binds to integrin  $\alpha_v\beta_3$  and compositions comprising this antibody. The antibodies can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. In some preferred embodiments, the anti- integrin  $\alpha_v\beta_3$  antibody of the invention is MEDI-522 (Vitaxin®). Vitaxin® and compositions or formulations comprising Vitaxin® are disclosed, *e.g.*, in International Publication Nos. WO 98/33919, WO 00/78815, and WO 02/070007; U.S. application Serial No. 09/339,222; U.S. Patent Application No. 10/091,236, filed March 4, 2002 and published November 12, 2002, as U.S. Pat. Pub. No. US 2002/0168360, each of which is incorporated herein by reference in its entirety.

[00247] In further embodiments, the antibody that immunospecifically binds to integrin  $\alpha_v\beta_3$  is not Vitaxin® or an antigen-binding fragment of Vitaxin®. Examples of known antibodies that immunospecifically bind to integrin  $\alpha_v\beta_3$  include, but are not limited to, 11D2 (Searle), the murine monoclonal LM609 (Scripps, International Publication Nos. WO 89/05155 and U.S. Patent No. 5,753,230, which is incorporated herein by reference in its entirety), International Publication Nos WO 98/33919 and WO 00/78815, each of which is incorporated herein by reference in its entirety), 17661-37E and 17661-37E 1-5 (USBiological), MON 2032 and 2033 (CalTag), ab7166 (BV3) and ab 7167 (BV4) (Abcam), and WOW-1 (Kiosses et al., Nature Cell Biology, 3:316-320).

[00248]  $\alpha_v\beta_3$ , an integrin has been found on new blood vessels as well as surface of many solid tumors, activated macrophages, monocytes, and osteoclasts. As the such, the anti- integrin



$\alpha_v\beta_3$  antibodies of this section can be used, for example, as an investigational antibody, or in the prevention or treatment of several destructive diseases.

[00249] The anti- integrin  $\alpha_v\beta_3$  antibodies of this section can be made, formulated, administered, used therapeutically or used prophylactically as described in U.S. Patent Application No. 10/091,236, filed March 4, 2002 and published November 12, 2002, as U.S. Pat. Pub. No. US 2002/0168360; U.S. Patent Application No. 10/769,712, filed January 30, 2004; U.S. Patent Application No. 10/769,720, filed January 30, 2004 and published September 9, 2004, as U.S. Pat. Pub. No. US 2004/0176272; U.S. Patent Application No. 10/379,145, filed March 4, 2003; U.S. Patent Application No. 10/379,189, filed March 4, 2003 and published as U.S. Pat. Pub. No. US 2004/0001835; PCT Application No. PCT/US04/02701, filed January 30, 2004; International Application Publication No.: WO 00/78815 A1, entitled "Anti-  $\alpha_v\beta_3$  recombinant human antibodies, nucleic acids encoding same and methods", by Huse et al.; and International Application Publication No.: WO 98/33919 A1, entitled "Anti-alpha-V-veta-3 recombinant humanized antibodies, nucleic acids encoding same and methods of use", by Huse et al.; International Publication No. WO 89/05155, the contents of which are hereby incorporated by reference in their entirety.

### **5.3.6 Antibodies that Immunospecifically Bind to CD2**

[00250] The formulations of the present invention comprise an isolated antibody that immunospecifically binds to CD2 and compositions comprising this antibody. The antibodies can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. In some preferred embodiments, the anti-CD2 antibody of the invention is sipilizumab (MEDI-507). Sipilizumab can selectively binds to cells expressing the CD2 antigen (specifically T cells, natural killer cells and thymocytes) and can be used, for example, in the prophylaxis and treatment of T cell lymphoma or other related conditions. MEDI-507 is disclosed, *e.g.*, in International Publication No. WO 99/03502, International Application Nos. PCT/US02/22273 and PCT/US02/06761, and U.S. Application Serial Nos. 09/462,140, 10/091,268, and 10/091,313, each of which is incorporated herein by reference in its entirety. MEDI-507 is a humanized IgG1 $\kappa$  class monoclonal antibody that immunospecifically binds to human CD2 polypeptide. MEDI-507 was constructed using molecular techniques to insert the CDRs from the rat monoclonal antibody LO-CD2a/BTI-322 into a human IgG1 framework. LO-CD2a/BTI-322 has the amino acid sequence disclosed, *e.g.*, in U.S. Patent Nos. 5,730,979, 5,817,311, and 5,951,983; and U.S. application Serial Nos. 09/056,072 and 09/462,140 (each of which is incorporated herein by reference in its entirety), or the amino acid sequence of the monoclonal antibody produced by the cell line deposited with the American Type Culture Collection

(ATCC®), 10801 University Boulevard, Manassas, Virginia 20110-2209 on July 28, 1993 as Accession Number HB 11423.

[00251] The anti- CD2 antibodies of this section can be made, formulated, administered, used therapeutically or prophylactically, or in other context as described in U.S. Patent Application No. 10/091,268, filed March 4, 2002, and published April 15, 2003, as U.S. Pat. Pub. No. US 2003/0068320; U.S. Patent Application No. 10/091,313, filed March 4, 2002, and published March 6, 2003, as U.S. Pat. Pub. No. US 2003/0044406; and U.S. Patent Application No. 10/657,006, filed September 5, 2003, and published December 30, 2004, as U.S. Pat. Pub. No. US 2004/0265315, the contents of which are hereby incorporated by reference in their entirety.

### **5.3.7 Antibodies that Immunoppecifically Bind to CD19**

[00252] The formulations of the present invention comprise an isolated antibody that immunospecifically binds to CD19 and a composition comprising this antibody. The antibodies can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. In some preferred embodiments, the anti-CD19 antibody of the invention is MT-103. MT-103 is the most-advanced clinical representative of a novel class of antibody derivatives called Bi-Specific T Cell Engagers (BiTE™). The BiTE compound MT-103 directs and activates the patient's own immune system against the cancer cells, stimulating T cells (a very potent type of white blood cell) to destroy B tumor cells (cancerous white blood cells). MT-103 specifically targets a particular protein (the CD19 antigen), which is present on cancerous B cells but not on other types of blood cells or healthy tissues, therefore avoiding the side effects of traditional chemotherapy

[00253] The anti- CD19 antibodies of this section can be made, formulated, administered, used therapeutically or prophylactically, or in other context as described in U.S. Pat. No. 6,723,538, and U.S. Pat. Pub. No. 2004/0162411.

[00254] The human CD19 molecule is a structurally distinct cell surface receptor that is expressed on the surface of human B cells. The invention relates to immunotherapeutic compositions and methods for the prophylaxis and treatment of GVHD, humoral rejection, and post-transplantation lymphoproliferative disorder in human subjects; autoimmune diseases and disorders; and cancers, using therapeutic antibodies that bind to the human CD19 antigen.

[00255] Hybridomas producing HB12a and HB12b anti-CD19 antibodies have been deposited under ATCC deposit nos. PTA-6580 and PTA-6581. See, also, U.S. Application No.

to be assigned (Attorney Docket No.: 11605-006-999) and U.S. Application No. 11/355,905, filed 2/15/2006, each of which is incorporated herein by reference in its entirety.

### 5.3.8 Antibodies that Immunoprecipitically Bind to EphA2

[00256] The formulations of the present invention comprise an isolated antibody that immunospecifically binds to EphA2 and a compositions comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. In some embodiments, the anti-EphA2 antibody of the invention is EA2. In some preferred embodiments, the EA2 antibody is human or humanized. In other embodiments, the is EA5. In some preferred embodiments, the EA5 antibody is human or humanized. Hybridomas producing the anti-EphA2 antibodies of the invention have been deposited with the American Type Culture Collection (ATCC, P.O. Box 1549, Manassas, VA 20108) under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedures, and assigned accession numbers, which are incorporated by reference, as shown in TABLE 4.

**TABLE 4:**

<b>EphA2 Antibodies</b>	<b>Deposit No.</b>	<b>Date of Deposit</b>
EA2.31	PTA-4380	May 22, 2002
EA5.12	PTA-4381	May 22, 2002
Eph099B-102.147	PTA-4572	August 7, 2002
Eph099B-208.261	PTA-4573	August 7, 2002
Eph099B-210.248	PTA-4574	August 7, 2002
Eph099B-233.152	PTA-5194	May 12, 2003
Eph101.530.241	PTA-4724	September 26, 2002

[00257] EphA2 is a 130 kDa receptor tyrosine kinase that is expressed in adult epithelia, where it is found at low levels and is enriched within sites of cell-cell adhesion (Zantek, et al, *Cell Growth & Differentiation* 10:629, 1999; Lindberg, et al., *Molecular & Cellular Biology* 10: 6316, 1990). EphA2 is upregulated on a large number of aggressive carcinoma cells. The anti-

EphA2 antibodies of this invention can be used, for example, in the treatment of a variety of tumors, including breast, colon, prostate, lung and skin cancers, as well as to prevent metastasis.

**[00258]** The anti-EphA2 antibodies of this section can be made, formulated, administered, used therapeutically or used prophylactically as described in U.S. Patent Application No. 10/823,259, filed April 12, 2004; U.S. Patent. Application No. 10/823,254, filed on April 12, 2004; U.S. Patent. Application No. 10/436,782, filed on May 12, 2003 and published February 12, 2004 as U.S. Pat. Pub. No. 2004/0028685; U.S. Patent. Application No. 10/436,783, filed on May 12, 2003 and published May 13, 2004 as U.S. Pat. Pub. No. 2004/0091486; U.S. Patent. Application No. 11/004,794, filed on December 3, 2004; U.S. Patent. Application No. 10/994,129, filed on November 19, 2004; U.S. Patent. Application No. 11/004,795, filed on December 3, 2004; and U.S. Provisional Application Nos. 60/662,517, 60/622,711, 60/622,489, filed October 27, 2004, the contents of which are hereby incorporated by reference in their entirety.

### **5.3.9 Antibodies that Immunoprecipitatively Bind to EphA4**

**[00259]** The formulations of the present invention comprise an isolated antibody that immunospecifically binds to an antigen of EphA4 and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. Hybridomas producing the anti-EphA4 antibodies of the invention have been deposited with the American Type Culture Collection (ATCC, P.O. Box 1549, Manassas, VA 20108) on June 4, 2004 under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedures, and assigned accession number PTA-6044 and PTA-4381 and incorporated by reference.

**[00260]** EphA4 is a receptor tyrosine kinase that is expressed in brain, heart, lung, muscle, kidney, placenta, pancreas (Fox, et al, *Oncogene* 10:897, 1995) and melanocytes (Easty, et al., *Int. J. Cancer* 71:1061, 1997). EphA4 is overexpressed in a number of cancers. The anti-EphA4 antibodies of this section can be used, for example, to decrease the expression of EphA4 in the treatment of pancreatic cancers etc.

**[00261]** The anti-EphA4 antibodies of this section can be made, formulated, administered, used therapeutically or used prophylactically as described in U.S. Patent Application No. 10/863,729, filed June 7, 2004; U.S. Patent. Application No. 11/004,794, filed on December 3,

2004; U.S. Patent. Application Nos. 11/004,794 and 11/004,795, filed on December 3, 2004, the contents of which are hereby incorporated by reference in their entirety.

#### **5.3.10 Antibodies that Immunopecifically Bind to IL-9**

[00262] The formulations of the present invention comprise an antibody that immunospecifically binds to IL-9 and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies. In some preferred embodiments, the anti-IL-9 antibodies is MEDI-528.

[00263] It has been shown that IL-9 may be a key mediator of asthma and may also contribute to other respiratory disorders including chronic obstructive pulmonary disease (COPD) and cystic fibrosis. The anti-IL-9 antibodies of this section may be used in the prophylaxis or treatment of asthma.

[00264] The anti-IL-9 antibodies of this section can be made, formulated, administered, used therapeutically or used prophylactically as described in U.S. Patent Application No. 10/823,253, filed April 12, 2004 and published January 6, 2005, as U.S. Pat. Pub. No. US 2005/0002934 A1; U.S. Patent. Application No. 10/823, 810, filed on April 12, 2004; U.S. Provisional Application Nos. 60/371,728 and 60,371, 683, filed April 12, 2002; and U.S. Provisional Application No. 60/561,845, filed April 12, 2004, the contents of which are hereby incorporated by reference in their entirety.

#### **5.3.11. Antibodies that Immunospecifically Bind to HMG1**

[00265] The formulations of the present invention can comprise an antibody that immunospecifically binds to HMG1 and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00266] The early proinflammatory cytokines (e.g., TNF, IL-1, etc.) mediate inflammation, and induce the late release of high mobility group protein 1 (HMG1) (also known as HMG-1, HMG1, and HMGB1), a protein that accumulates in serum and mediates delayed lethality and further induction of early proinflammatory cytokines.

[00267] It has also been shown that HMG1 can be actively secreted by stimulated macrophages or monocytes in a process requiring acetylation of the molecule, which enables

translocation from the nucleus to secretory lysosomes and results in the secretion of an acetylated form of HMG1. *See*, PCT/IB2003/005718. Thus, HMG1 passively released from necrotic cells and HMGB1 actively secreted by inflammatory cells are molecularly different.

[00268] Further, HMG1 has been implicated as a cytokine mediator of delayed lethality in endotoxemia. *See, e.g.*, U.S. patents 6,468,533 and 6,448,223. More specifically, it has been demonstrated that bacterial endotoxin (lipopolysaccharide (LPS)) activates monocytes/macrophages to release HMG1 as a late response to activation, resulting in elevated serum HMG1 levels that are toxic. Antibodies against HMG1 have been shown to prevent lethality of endotoxin even when antibody administration is delayed until after the early cytokine response. Like other proinflammatory cytokines, HMG1 is a potent activator of monocytes. Intratracheal application of HMG1 causes acute lung injury, and anti-HMG1 antibodies protect against endotoxin-induced lung edema. In addition, serum HMG1 levels are elevated in critically ill patients with sepsis or hemorrhagic shock, and levels are significantly higher in non-survivors as compared to survivors.

[00269] The anti-HMG1 antibodies of this section can be made, formulated, administered, used therapeutically or used prophylactically as described in U.S. Patent Publication No. 2006-0099207 A1 filed October 21, 2005, which is incorporated herein by reference in its entirety. Three clones, S6, S16 and G4 have been deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, Va. 20110-2209) and assigned ATCC Deposit Nos. PTA-6143 (Deposited August 4, 2004), PTA-6259 (Deposited October 19, 2004) and PTA-6258 (Deposited October 19, 2004) (also referred to herein as “S6”, “S16”, and “G4”, respectively) as described in U.S. Patent Publication No. 2006-0099207 A1 filed October 21, 2005, which is incorporated herein by reference in its entirety.

#### **5.3.12. Antibodies that Immunospecifically Bind to ALK**

[00270] The formulations of the present invention can comprise an antibody that immunospecifically binds to ALK and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00271] Monoclonal antibodies against ALK as well as hybridoma cell lines producing ALK monoclonal antibodies 8B10, 16G2-3 and 9C10-5 (deposited with the American Type Culture Collection (10801 University Boulevard, Manassas, Va. 20110-2209) and assigned ATCC Deposit Nos. to be assigned, respectively) as described in U.S. Patent Application No.

09/880,097, filed 06-14-2001 and published March 21, 2002, as U.S. Pat. Pub. No. 20020034768, which is incorporated herein by reference in its entirety.

[00272] Pleiotrophin (PTN) is a 136-amino acid, secreted, heparin-binding cytokine that has diverse functions including a role in angiogenesis. PTN has been shown to specifically bind to a receptor tyrosine kinase, Anaplastic Lymphoma Kinase (ALK), and such binding leads to auto-phosphorylation of the receptor and subsequent phosphorylation of a number of signal transduction molecules such as IRS-1, PLC-gamma, PI3 kinase, and Shc, and activates a cell survival pathway. See PCT Pat. App. Pub. No. WO 01/96364. Accordingly, agents and therapeutic treatments that regulate ALK-mediated signal transduction pathways can affect one or more ALK-regulated functions, including, for example, angiogenesis. ALK participates in various disease states, including cancers and diseases related to unwanted or excessive angiogenesis. Additionally, ALK participates in a desirable way in certain processes, such as wound healing. ALK and/or PTN are expressed, often at high levels, in a variety of tumors. Therefore, agents that downregulate ALK and/or PTN function may affect tumors by a direct effect on the tumor cells, an indirect effect on the angiogenic processes recruited by the tumor, or a combination of direct and indirect effects.

### 5.3.13. Antibodies that Immunospecifically Bind to CD20

[00273] The formulations of the present invention can comprise an antibody that immunospecifically binds to CD20 and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00274] CD20 is only expressed by B lymphocytes (Stashenko et al. (1980) *J Immunol* 125:1678-1685; Tedder et al., 1988a). CD20 forms a homo- or hetero-tetrameric complex that is functionally important for regulating cell cycle progression and signal transduction in B lymphocytes (Tedder and Engel, 1994). CD20 additionally regulates transmembrane  $\text{Ca}^{++}$  conductance, possibly as a functional component of a  $\text{Ca}^{++}$ -permeable cation channel (Bubien et al. *J Cell Biol* 121:1121-1132; Kanzaki et al. (1997a) *J Biol Chem* 272:14733-14739; Kanzaki et al. (1997b) *J Biol Chem* 272:4964-4969; Kanzaki et al. (1995) *J Biol Chem* 270:13099-13104). Antibodies against CD20 are effective in treating non-Hodgkin's lymphoma (McLaughlin et al. (1998) *Oncology* 12:1763-1769; Onrust et al. (1989) *J Biol Chem* 264:15323-15327; Weiner (1999) *Semin Oncol* 26:43-51).

See, also, US Patent Application No. 10/433,287, filed September 30, 2003, published as US 20040137566 on July 15, 2004, which is incorporated herein by reference in its entirety.

#### **5.3.14. Antibodies that Immunospecifically Bind to CD22**

[00275] The formulations of the present invention can comprise an antibody that immunospecifically binds to CD22 and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00276] Anti-CD22 antibodies have been described, for example, in U.S. Pat. Nos. 5,484,892; 6,183,744; 6,187,287; 6,254,868; 6,306,393, and in Tuscano *et al.*, *Blood* 94(4):1382-92 (1999) (each of which is incorporated herein in its entirety by reference). The use of monoclonal antibodies, including anti-CD22 antibodies, in the treatment of non-Hodgkin's lymphoma is reviewed, for example, by Renner *et al.*, *Leukemia* 11(Suppl. 2):S5509 (1997).

[00277] The use of humanized CD22 antibodies has been described for the treatment of autoimmune disorders (*see*, Tedder U.S. Patent Application Publication No. US2003/0202975) and for the treatment of B cell malignancies, such as lymphomas and leukemias (*see*, Tuscano U.S. Patent Application Publication No. U.S. 2004/0001828). Humanized CD22 antibodies that target specific epitopes on CD22 have been described for use in immunoconjugates for therapeutic uses in cancer (*see* U.S. Patent Nos. 5,789,554 and 6,187,287 to Leung).

[00278] Exemplary VH and VK antibody regions of the invention were deposited with the American Type Culture Collection (ATCC). In particular, a plasmid encoding the humanized anti-CD22 VH sequence of the invention designated RHOv2 was deposited under ATCC deposit no. PTA-7372, on February 9, 2006. A plasmid encoding the humanized anti-CD22 VH sequence of the invention designated RHOv2ACD was deposited under ATCC deposit no. PTA-7373, on February 9, 2006. A plasmid encoding the humanized anti-CD22 VK sequence of the invention, RKA was deposited under ATCC deposit no. PTA-7370, on February 9, 2006. A plasmid encoding the humanized anti-CD22 VK sequence of the invention, RKC, was deposited under ATCC deposit no. PTA-7371, on February 9, 2006.

[00279] See, also, U.S. Provisional Application No. TBA, filed March 6, 2006, attorney docket no. BC320P1, which is incorporated herein by reference in its entirety.

#### **5.3.15. Antibodies that Immunospecifically Bind to Chitinase**



[00280] The formulations of the present invention can comprise an antibody that immunospecifically binds to Chitinase and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00281] It is described that blocking a chitinase/chitinase-like protein, in vivo results in protection of bone and cartilage as well as a reduction in weight loss in a mouse RA model. These results support the role of chitinase/chitinase-like proteins in chronic inflammatory diseases and more specifically the role of chitinase/chitinase-like proteins in OCL-related diseases including bone metabolism and connective tissue disorders and diseases. Furthermore, these results validate human chitinase/chitinase-like proteins as potential therapeutic targets for the prevention and treatment of OCL-related diseases.

[00282] See, also, U.S. Application No. 10/202,436, filed July 23, 2002, published as US 20030049261 on March 13, 2003, which is incorporated herein by reference in its entirety.

#### **5.3.16. Antibodies that Immunospecifically Bind to Interferon alpha**

[00283] The formulations of the present invention can comprise an antibody that immunospecifically binds to interferon alpha and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00284] The invention provides a method of treating an interferon alpha-mediated disease or disorder in a subject, comprising administering to the subject an anti-IFN alpha antibody of the invention, such that the interferon-alpha mediated disease in the subject is treated. Examples of diseases that can be treated include autoimmune diseases (*e.g.*, systemic lupus erythematosus, multiple sclerosis, insulin dependent diabetes mellitus, inflammatory bowel disease, psoriasis, autoimmune thyroiditis, rheumatoid arthritis and glomerulonephritis), transplant rejection and graft versus host disease.

[00285] Anti-interferon alpha monoclonal antibody has also been described in U.S. serial no. 11/009,410 filed December 10, 2004, which is incorporated herein by reference in its entirety.

#### **5.3.17. Antibodies that Immunospecifically Bind to Interferon alpha receptor**

[00286] The formulations of the present invention can comprise an antibody that immunospecifically binds to interferon alpha receptor and a composition comprising this antibody. The antibodies of the invention can be monoclonal antibodies, human antibodies, humanized antibodies or chimeric antibodies.

[00287] The invention also provides a method for inhibiting biological activity of a type I interferon on a cell expressing interferon alpha receptor 1 comprising contacting the cell with the antibody of the invention, such that the biological activity of the type I interferon is inhibited. The invention also provides a method of treating a type I interferon-mediated disease or disorder in a subject in need of treatment comprising administering to the subject the antibody, or antigen-binding portion thereof, of the invention, such that the type-I interferon mediated disease in the subject is treated. The type I interferon-mediated disease can be, for example, an interferon alpha-mediated disease.

[00288] Examples of disease or disorders that can be treated using the methods of the invention include systemic lupus erythematosus, insulin dependent diabetes mellitus, inflammatory bowel disease, multiple sclerosis, psoriasis, autoimmune thyroiditis, rheumatoid arthritis, glomerulonephritis, HIV infection, AIDS, transplant rejection and graft versus host disease.

[00289] Anti-interferon receptor monoclonal antibody has been described in U.S. Patent Publication No. 2006-0029601 A1, published 2/9/2006, filed June 20, 2005, which is incorporated herein by reference in its entirety.

### **5.3.18 Antibodies That Have Therapeutic Utility**

[00290] The formulations of the present invention comprise antibodies that have therapeutic utility, including but not limited to antibodies listed in Table 5.

[00291] TABLE 5. THERAPEUTIC ANTIBODIES THAT CAN BE USED IN CONNECTION WITH THE PRESENT INVENTION

<b>Company</b>	<b>Product</b>	<b>Disease</b>	<b>Target</b>
Abgenix AltaRex	ABX-EGF OvaRex BravaRex	Cancer ovarian cancer metastatic cancers	EGF receptor tumor antigen CA125 tumor antigen MUC1
Antisoma	Theragyn (pentumomabyrrium-90)	ovarian cancer	PEM antigen

Company	Product	Disease	Target
	Therex	breast cancer	PEM antigen
Boehringer Ingelheim	Blvatuzumab	head & neck cancer	CD44
Centocor/J&J	Panorex	Colorectal cancer	17-1A
	ReoPro	PTCA	Gp IIIb/IIIa
	ReoPro	Acute MI	Gp IIIb/IIIa
	ReoPro	Ischemic stroke	Gp IIIb/IIIa
Corixa	Bexocar	NHL	CD20
CRC Technology	MAB, idiotypic 105AD7	colorectal cancer vaccine	Gp72
Crucell	Anti-EpCAM	cancer	Ep-CAM
Cytoclonal	MAB, lung cancer	non-small cell lung cancer	NA
Genentech	Herceptin	metastatic breast cancer	HER-2
	Herceptin	early stage breast cancer	HER-2
	Rituxan	Relapsed/refract ory low-grade or follicular NHL	CD20
	Rituxan	intermediate & high-grade NHL	CD20
	MAB-VEGF	NSCLC, metastatic	VEGF
	MAB-VEGF	Colorectal cancer, metastatic	VEGF
	AMD Fab	age-related macular degeneration	CD18
	E-26 (2 <sup>nd</sup> gen. IgE)	allergic asthma & rhinitis	IgE
IDEC	Zevalin (Rituxan + yttrium-90)	low grade of follicular, relapsed or refractory, CD20-positive, B-cell NHL and Rituximab- refractory NHL	CD20
ImClone	Cetuximab + innotecan	refractory colorectal carcinoma	EGF receptor
	Cetuximab + cisplatin & radiation	newly diagnosed or recurrent head & neck cancer	EGF receptor
	Cetuximab + gemcitabine	newly diagnosed metastatic	EGF receptor

Company	Product	Disease	Target
	Cetuximab + cisplatin + 5FU or Taxol	pancreatic carcinoma recurrent or metastatic head & neck cancer	EGF receptor
	Cetuximab + carboplatin + paclitaxel	newly diagnosed non-small cell lung carcinoma	EGF receptor
	Cetuximab + cisplatin	head & neck cancer (extensive incurable local-regional disease & distant metastases)	EGF receptor
	Cetuximab + radiation	locally advanced head & neck carcinoma	EGF receptor
	BEC2 + Bacillus Calmette Guerin	small cell lung carcinoma	mimics ganglioside GD3
	BEC2 + Bacillus Calmette Guerin	melanoma	mimics ganglioside GD3
	IMC-1C11	colorectal cancer with liver metastases	VEGF-receptor
ImmonoGen	nuC242-DM1	Colorectal, gastric, and pancreatic cancer	nuC242
ImmunoMedics	LymphoCide	Non-Hodgkins lymphoma	CD22
	LymphoCide Y-90	Non-Hodgkins lymphoma	CD22
	CEA-Cide	metastatic solid tumors	CEA
	CEA-Cide Y-90	metastatic solid tumors	CEA
	CEA-Scan (Tc-99m-labeled arcitumomab)	colorectal cancer (radioimaging)	CEA
	CEA-Scan (Tc-99m-labeled arcitumomab)	Breast cancer (radioimaging)	CEA
	CEA-Scan (Tc-99m-labeled arcitumomab)	lung cancer (radioimaging)	CEA
	CEA-Scan (Tc-99m-labeled arcitumomab)	intraoperative tumors (radio imaging)	CEA
	LeukoScan (Tc-99m-labeled sulesomab)	soft tissue infection (radioimaging)	CEA

Company	Product	Disease	Target
	LymphoScan (Tc-99m-labeled)	lymphomas (radioimaging)	CD22
	AFP-Scan (Tc-99m-labeled)	liver 7 gem-cell cancers (radioimaging)	AFP
Intracel	HumaRAD-HN (+ yttrium-90)	head & neck cancer	NA
	HumaSPECT	colorectal imaging	NA
Medarex	MDX-101 (CTLA-4)	Prostate and other cancers	CTLA-4
	MDX-210 (her-2 overexpression)	Prostate cancer	HER-2
	MDX-210/MAK	Cancer	HER-2
MedImmune	Vitaxin	Cancer	$\alpha v \beta_3$
Merck KGaA	MAb 425	Various cancers	EGF receptor
	IS-IL-2	Various cancers	Ep-CAM
Millennium	Campath (alemtuzumab)	chronic lymphocytic leukemia	CD52
NeoRx	CD20-streptavidin (+ biotin-yttrium 90)	Non-Hodgkins lymphoma	CD20
	Avidicin (albumin + NRLU13)	metastatic cancer	NA
Peregrine	Oncolym (+ iodine-131)	Non-Hodgkins lymphoma	HLA-DR 10 beta
	Cotara (+ iodine-131)	unresectable malignant glioma	DNA-associated proteins
Pharmacia Corporation	C215 (+ staphylococcal enterotoxin)	pancreatic cancer	NA
	MAb, lung/kidney cancer	lung & kidney cancer	NA
	nacalomab tafenatox (C242 + staphylococcal enterotoxin)	colon & pancreatic cancer	NA
Protein Design Labs	Nuvion	T cell malignancies	CD3
	SMART M195	AML	CD33
	SMART 1D10	NHL	HLA-DR antigen
Titan	CEAVac	colorectal cancer, advanced metastatic melanoma & small cell lung cancer	CEA
	TriGem	metastatic melanoma & small cell lung cancer	GD2-ganglioside
	TriAb	metastatic breast	MUC-1

Company	Product	Disease	Target
Trilex	CEAVac	cancer colorectal cancer, advanced	CEA
	TriGem	metastatic melanoma & small cell lung cancer	GD2-ganglioside
	TriAb	metastatic breast cancer	MUC-1
Viventia Biotech	NovoMAb-G2 radiolabeled	Non-Hodgkins lymphoma	NA
	Monopharm C	colorectal & pancreatic carcinoma	SK-1 antigen
	GlioMAb-H (+ gelonin toxin)	glioma, melanoma & neuroblastoma	NA
Xoma	Rituxan	Relapsed/refractory low-grade or follicular NHL	CD20
	Rituxan	intermediate & high-grade NHL	CD20
	ING-1	adenomcarcino ma	Ep-CAM

### **5.3.19. Antibodies That Can Be Used For Inflammatory Disorders or Autoimmune Diseases**

[00292] The formulations of the present invention further comprises any of the antibodies known in the art for the treatment and/or prevention of autoimmune disease or inflammatory disease. A non-limiting example of the antibodies that are used for the treatment or prevention of inflammatory disorders which can be engineered according to the invention is presented in Table 6A, and a non-limiting example of the antibodies that are used for the treatment or prevention of autoimmune disorder is presented in Table 6B.

[00293] TABLE 6A: ANTIBODIES FOR INFLAMMATORY DISEASES AND AUTOIMMUNE DISEASES THAT CAN USED IN ACCORDANCE WITH THE INVENTION.

Antibody Name	Target Antigen	Product Type	Isotype	Sponsors	Indication
5G1.1	Complement (C5)	Humanized	IgG	Alexion Pharm Inc	Rheumatoid Arthritis
5G1.1	Complement (C5)	Humanized	IgG	Alexion Pharm Inc	SLE

Antibody Name	Target Antigen	Product Type	Isotype	Sponsors	Indication
5G1.1	Complement (C5)	Humanized	IgG	Alexion Pharm Inc	Nephritis
5G1.1-SC	Complement (C5)	Humanized	ScFv	Alexion Pharm Inc	Cardiopulmonary Bypass
5G1.1-SC	Complement (C5)	Humanized	ScFv	Alexion Pharm Inc	Myocardial Infarction
5G1.1-SC	Complement (C5)	Humanized	ScFv	Alexion Pharm Inc	Angioplasty
ABX-CBL	CBL	Human		Abgenix Inc	GvHD
ABX-CBL	CD147	Murine	IgG	Abgenix Inc	Allograft rejection
ABX-IL8	IL-8	Human	IgG2	Abgenix Inc	Psoriasis
Antegren	VLA-4	Humanized	IgG	Athena/Elan	Multiple Sclerosis
Anti-CD11a	CD11a	Humanized	IgG1	Genentech Inc/Xoma	Psoriasis
Anti-CD18	CD18	Humanized	Fab'2	Genentech Inc	Myocardial infarction
Anti-LFA1	CD18	Murine	Fab'2	Pasteur-Merieux/ Immunotech	Allograft rejection
Antova	CD40L	Humanized	IgG	Biogen	Allograft rejection
Antova	CD40L	Humanized	IgG	Biogen	SLE
BTI-322	CD2	Rat	IgG	Medimmune Inc	GvHD, Psoriasis
CDP571	TNF-alpha	Humanized	IgG4	Celltech	Crohn's
CDP571	TNF-alpha	Humanized	IgG4	Celltech	Rheumatoid Arthritis
CDP850	E-selectin	Humanized		Celltech	Psoriasis
Corsevin M	Fact VII	Chimeric		Centocor	Anticoagulant
D2E7	TNF-alpha	Human		CAT/BASF	Rheumatoid Arthritis
Hu23F2G	CD11/18	Humanized		ICOS Pharm Inc	Multiple Sclerosis
Hu23F2G	CD11/18	Humanized	IgG	ICOS Pharm Inc	Stroke
IC14	CD14			ICOS Pharm Inc	Toxic shock
ICM3	ICAM-3	Humanized		ICOS Pharm Inc	Psoriasis
IDEC-114	CD80	Primatised		IDEC Pharm/Mitsubishi	Psoriasis
IDEC-131	CD40L	Humanized		IDEC Pharm/Eisai	SLE
IDEC-131	CD40L	Humanized		IDEC Pharm/Eisai	Multiple Sclerosis
IDEC-151	CD4	Primatised	IgG1	IDEC Pharm/Glaxo SmithKline	Rheumatoid Arthritis

Antibody Name	Target Antigen	Product Type	Isotype	Sponsors	Indication
IDEC-152	CD23	Primatised		IDEC Pharm	Asthma/Allergy
Infliximab	TNF-alpha	Chimeric	IgG1	Centocor	Rheumatoid Arthritis
Infliximab	TNF-alpha	Chimeric	IgG1	Centocor	Crohn's
LDP-01	beta2-integrin	Humanized	IgG	Millennium Inc (LeukoSite Inc.)	Stroke
LDP-01	beta2-integrin	Humanized	IgG	Millennium Inc (LeukoSite Inc.)	Allograft rejection
LDP-02	alpha4beta7	Humanized		Millennium Inc (LeukoSite Inc.)	Ulcerative Colitis
MAK-195F	TNF alpha	Murine	Fab'2	Knoll Pharm, BASF	Toxic shock
MDX-33	CD64 (FcR)	Human		Medarex/Cent eon	Autoimmune haematological disorders
MDX-CD4	CD4	Human	IgG	Medarex/Eisai / Genmab	Rheumatoid Arthritis
MEDI-507	CD2	Humanized		Medimmune Inc	Psoriasis
MEDI-507	CD2	Humanized		Medimmune Inc	GvHD
OKT4A	CD4	Humanized	IgG	Ortho Biotech	Allograft rejection
OrthoClone OKT4A	CD4	Humanized	IgG	Ortho Biotech	Autoimmune disease
Orthoclone / anti-CD3 OKT3	CD3	Murine	mIgG2a	Ortho Biotech	Allograft rejection
RepPro/ Abciximab	gpIIbIIIa	Chimeric	Fab	Centocor/Lilly	Complications of coronary angioplasty
rhuMab-E25	IgE	Humanized	IgG1	Genentech/Novartis/Tanox Biosystems	Asthma/Allergy
SB-240563	IL5	Humanized		GlaxoSmithKline	Asthma/Allergy
SB-240683	IL-4	Humanized		GlaxoSmithKline	Asthma/Allergy
SCH55700	IL-5	Humanized		Celltech/Schering	Asthma/Allergy
Simulect	CD25	Chimeric	IgG1	Novartis Pharm	Allograft rejection



Antibody Name	Target Antigen	Product Type	Isotype	Sponsors	Indication
SMART a-CD3	CD3	Humanized		Protein Design Lab	Autoimmune disease
SMART a-CD3	CD3	Humanized		Protein Design Lab	Allograft rejection
SMART a-CD3	CD3	Humanized	IgG	Protein Design Lab	Psoriasis
Zenapax	CD25	Humanized	IgG1	Protein Design Lab/Hoffman-La Roche	Allograft rejection

TABLE 6B: ANTIBODIES FOR AUTOIMMUNE DISORDERS THAT CAN BE USED IN ACCORDANCE WITH THE INVENTION

Antibody	Indication	Target Antigen
<b>ABX-RB2</b>		antibody to CBL antigen on T cells, B cells and NK cells fully human antibody from the Xenomouse
<b>5c8 (Anti CD-40 ligand antibody)</b>	Phase II trials were halted in Oct. 99 examine "adverse events"	CD-40
<b>IDEC 131</b>	systemic lupus erythematous (SLE)	anti CD40 humanized
<b>IDEC 151</b>	rheumatoid arthritis	primatized ; anti-CD4
<b>IDEC 152</b>	Asthma	primatized; anti-CD23
<b>IDEC 114</b>	Psoriasis	primatized anti-CD80
<b>MEDI-507</b>	rheumatoid arthritis; multiple sclerosis Crohn's disease Psoriasis	anti-CD2
<b>LDP-02 (anti-b7 mAb)</b>	inflammatory bowel disease Chron's disease ulcerative colitis	a4b7 integrin receptor on white blood cells (leukocytes)
<b>SMART Anti-Gamma Interferon antibody</b>	autoimmune disorders	Anti-Gamma Interferon
<b>Verteportin</b>	rheumatoid arthritis	
<b>MDX-33</b>	blood disorders caused by autoimmune reactions Idiopathic Thrombocytopenia Purpurea (ITP)	monoclonal antibody against FcRI receptors

Antibody	Indication	Target Antigen
	autoimmune hemolytic anemia	
<b>MDX-CD4</b>	treat rheumatoid arthritis and other autoimmunity	monoclonal antibody against CD4 receptor molecule
<b>VX-497</b>	autoimmune disorders multiple sclerosis rheumatoid arthritis inflammatory bowel disease lupus psoriasis	inhibitor of inosine monophosphate dehydrogenase (enzyme needed to make new RNA and DNA used in production of nucleotides needed for lymphocyte proliferation)
<b>VX-740</b>	rheumatoid arthritis	inhibitor of ICE interleukin-1 beta (converting enzyme controls pathways leading to aggressive immune response)
<b>VX-745</b>	specific to inflammation involved in chemical signalling of immune response onset and progression of inflammation	inhibitor of P38MAP kinase mitogen activated protein kinase
<b>Enbrel (etanercept)</b>		targets TNF (tumor necrosis factor)
<b>IL-8</b>		fully human monoclonal antibody against IL-8 (interleukin 8)
<b>Apogen MP4</b>		recombinant antigen selectively destroys disease associated T-cells induces apoptosis T-cells eliminated by programmed cell death no longer attack body's own cells specific apogens target specific T-cells

#### 5.4 Methods of Producing Antibodies

[00294] The antibodies used in the present invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[00295] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a

combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term “monoclonal antibody” as used herein is not limited to antibodies produced through hybridoma technology. The term “monoclonal antibody” refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

**[00296]** Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. Briefly, mice can be immunized with an antigen (either the full length protein or a domain thereof, *e.g.*, the extracellular or the ligand binding domain) and once an immune response is detected, *e.g.*, antibodies specific for the particular antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. Hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

**[00297]** Accordingly, monoclonal antibodies can be generated by culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with the antigen with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind the antigen.

**[00298]** Antibody fragments used in the present invention may be generated by any technique known to those of skill in the art. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. Further, the antibodies of the present invention can also be generated using various phage display methods known in the art.

**[00299]** In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of lymphoid tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector (*e.g.*, p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an epitope of interest can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., 1995, *J. Immunol. Methods* 182:41-50; Ames et al., 1995, *J. Immunol. Methods* 184:177; Kettleborough et al., 1994, *Eur. J. Immunol.* 24:952-958; Persic et al., 1997, *Gene* 187:9; Burton et al., 1994, *Advances in Immunology* 57:191-280; International Application No. PCT/GB91/01134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

**[00300]** Phage may be screened for antigen binding activities. As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in International Publication No. WO 92/22324; Mullinax et al., 1992, *BioTechniques* 12:864; Sawai et al., 1995, *AJRI* 34:26; and Better et al., 1988, *Science* 240:1041 (said references incorporated by reference in their entireties).

**[00301]** To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH

constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise an EF-1 $\alpha$  promoter, a secretion signal, a cloning site for the variable domain, constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

**[00302]** For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also U.S. Patent Nos. 4,444,887 and 4,716,111; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

**[00303]** Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J<sub>H</sub> region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell

differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, International Publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Fremont, CA) and Medarex (Princeton, NJ) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

**[00304]** A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a non-human antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. *See, e.g.*, Morrison, 1985, *Science* 229:1202; Oi et al., 1986, *BioTechniques* 4:214; Gillies et al., 1989, *J. Immunol. Methods* 125:191-202; and U.S. Patent Nos. 6,311,415, 5,807,715, 4,816,567, and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from a non-human species and framework regions from a human immunoglobulin molecule can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, *Molecular Immunology* 28(4/5):489-498; Studnicka et al., 1994, *Protein Engineering* 7:805; and Roguska et al., 1994, *PNAS* 91:969), and chain shuffling (U.S. Patent No. 5,565,332).

**[00305]** Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (*See, e.g.*, U.S. Patent No. 5,585,089; and Riechmann et al., 1988, *Nature* 332:323, which are incorporated herein by reference in their entireties.)

**[00306]** A humanized antibody is an antibody or its variant or fragment thereof which is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and a CDR having substantially the amino acid sequence of a non-human immunoglobulin. A humanized antibody comprises substantially all of at least one, and typically two, variable domains in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (*i.e.*, donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub> and IgG<sub>4</sub>. Usually the constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the class is typically IgG<sub>1</sub>. Where such cytotoxic activity is not desirable, the constant domain may be of the IgG<sub>2</sub> class. The humanized antibody may comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, *e.g.*, the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the import antibody. Such mutations, however, will not be extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental framework region (FR) and CDR sequences, more often 90%, and most preferably greater than 95%. Humanized antibodies can be produced using variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, *Molecular Immunology* 28(4/5):489-498; Studnicka et al., 1994, *Protein Engineering* 7(6):805-814; and Roguska et al., 1994, *PNAS* 91:969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.*, U.S. Patent Nos. 6,407,213, 5,766,886, 5,585,089, International Publication No. WO 9317105, Tan et al., 2002, *J. Immunol.* 169:1119-25, Caldas et al., 2000, *Protein Eng.* 13:353-60, Morea et al., 2000, *Methods* 20:267-79, Baca et al., 1997, *J. Biol. Chem.* 272:10678-84, Roguska et al., 1996, *Protein Eng.* 9:895-904, Couto et al., 1995, *Cancer Res.* 55

(23 Supp):5973s-5977s, Couto et al., 1995, *Cancer Res.* 55:1717-22, Sandhu, 1994, *Gene* 150:409-10, Pedersen et al., 1994, *J. Mol. Biol.* 235:959-73, Jones et al., 1986, *Nature* 321:522-525, Riechmann et al., 1988, *Nature* 332:323, and Presta, 1992, *Curr. Op. Struct. Biol.* 2:593-596. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen et al., U.S. Patent No. 5,585,089; and Riechmann et al., 1988, *Nature* 332:323, which are incorporated herein by reference in their entireties.)

[00307] Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotypic antibodies using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1989, *FASEB J.* 7:437-444; and Nissinoff, 1991, *J. Immunol.* 147:2429-2438). The invention provides methods employing the use of polynucleotides comprising a nucleotide sequence encoding an antibody of the invention or a fragment thereof.

#### **5.4.1 Recombinant Expression Of An Antibody**

[00308] Recombinant expression of an antibody used in the invention, a derivative, analog or fragment thereof, (*e.g.*, a heavy or light chain of an antibody of the invention or a portion thereof or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a portion thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, *e.g.*, International Publication Nos.



WO 86/05807 and WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

**[00309]** The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention or fragments thereof, or a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

**[00310]** A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention (see, *e.g.*, U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, NS0, and 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., 1986, *Gene*

45:101; and Cockett et al., 1990, *BioTechnology* 8:2). In a specific embodiment, the expression of nucleotide sequences encoding antibodies or fragments thereof which immunospecifically bind to and agonize is regulated by a constitutive promoter, inducible promoter or tissue specific promoter.

**[00311]** In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., 1983, *EMBO* 12:1791), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, *Nucleic Acids Res.* 13:3101-3109; Van Heeke & Schuster, 1989, *J. Biol. Chem.* 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

**[00312]** In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

**[00313]** In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (e.g., see Logan & Shenk, 1984, *PNAS* 81:355-359). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and

adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, *e.g.*, Bittner et al., 1987, *Methods in Enzymol.* 153:516-544).

**[00314]** In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT20, NS1, T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7030 and HsS78Bst cells.

**[00315]** The antibodies comprising at least one zero-order thioether can be recombinantly produced by any cell lines for producing antibodies known to those skilled in the art. It has been found that it is advantageous to produce the antibodies of the invention in melanoma cells. In certain embodiments, the antibodies of the invention are recombinantly produced in melanoma cells. In some embodiments, the antibodies of the invention are not recombinantly produced in CHO cell line. In other embodiments, the antibodies of the invention are not recombinantly produced in NS0 cell line.

**[00316]** For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows

cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

**[00317]** A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler et al., 1977, *Cell* 11:223), glutamine synthase, hypoxanthine guanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, *Proc. Natl. Acad. Sci. USA* 48:202), and adenine phosphoribosyltransferase (Lowy et al., 1980, *Cell* 22:8-17) genes can be employed in tk-, gs-, hgpri- or apri- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler et al., 1980, *PNAS* 77:357; O'Hare et al., 1981, *PNAS* 78:1527); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, *PNAS* 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Wu and Wu, 1991, *Biotherapy* 3:87; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573; Mulligan, 1993, *Science* 260:926; and Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62: 191; May, 1993, *TIB TECH* 11:155-); and *hygro*, which confers resistance to hygromycin (Santerre et al., 1984, *Gene* 30:147). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression; A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., 1981, *J. Mol. Biol.* 150:1, which are incorporated by reference herein in their entireties.

**[00318]** The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., 1983, *Mol. Cell. Biol.* 3:257).

**[00319]** The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a

light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, 1986, *Nature* 322:52; and Kohler, 1980, *PNAS* 77:2197). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

**[00320]** Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention or fragments thereof may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

### **5.5 Use of the antibodies and compositions of the present invention**

**[00321]** The formulations comprising antibodies and compositions thereof can be used in any context that those of skilled in the art recognize. For example, the formulations of the invention can be used directly against a particular antigen. The formulations of the invention comprising antibodies and compositions can also be used in diagnostic assays either *in vivo* or *in vitro* for detection/identification of the expression of an antigen in a subject or a biological sample (*e.g.*, cells or tissues). Formulations of the invention comprising antibodies and compositions can be used alone or in combination with other prophylactic or therapeutic agents for treating, managing, preventing or ameliorating a disorder or one or more symptoms thereof.

**[00322]** The present invention provides methods for preventing, managing, treating, or ameliorating a disorder comprising administering to a subject in need thereof one or more antibodies of the invention alone or in combination with one or more therapies (*e.g.*, one or more prophylactic or therapeutic agents) other than an antibody of the invention. The present invention also provides formulations comprising one or more antibodies of the invention and one or more prophylactic or therapeutic agents other than antibodies of the invention and methods of preventing, managing, treating, or ameliorating a disorder or one or more symptoms thereof utilizing said compositions. Therapeutic or prophylactic agents include, but are not limited to, small molecules, synthetic drugs, peptides, polypeptides, proteins, nucleic acids (*e.g.*,

DNA and RNA nucleotides including, but not limited to, antisense nucleotide sequences, triple helices, RNAi, and nucleotide sequences encoding biologically active proteins, polypeptides or peptides) antibodies, synthetic or natural inorganic molecules, mimetic agents, and synthetic or natural organic molecules.

**[00323]** Any therapy which is known to be useful, or which has been used or is currently being used for the prevention, management, treatment, or amelioration of a disorder or one or more symptoms thereof can be used in combination with an antibody or a composition of the invention in accordance with the invention described herein. See, e.g., Gilman et al., Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill, New York, 2001; The Merck Manual of Diagnosis and Therapy, Berkow, M. D. et al. (eds.), 17th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, N.J., 1999; Cecil Textbook of Medicine, 20th Ed., Bennett and Plum (eds.), W. B. Saunders, Philadelphia, 1996 for information regarding therapies (e.g., prophylactic or therapeutic agents) which have been or are currently being used for preventing, treating, managing, or ameliorating a disorder or one or more symptoms thereof. Examples of such agents include, but are not limited to, immunomodulatory agents, anti-inflammatory agents (e.g., adrenocorticoids, corticosteroids (e.g., beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, methylprednisolone, prednisolone, prednisone, hydrocortisone), glucocorticoids, steroids, non-steroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen, diclofenac, and COX-2 inhibitors), anti-cancer agents, pain relievers, leukotriene antagonists (e.g., montelukast, methyl xanthines, zafirlukast, and zileuton), beta2-agonists (e.g., albuterol, biterol, fenoterol, isoetharine, metaproterenol, pirbuterol, salbutamol, terbutalin formoterol, salmeterol, and salbutamol terbutaline), anticholinergic agents (e.g., ipratropium bromide and oxitropium bromide), sulphasalazine, penicillamine, dapsone, antihistamines, anti-malarial agents (e.g., hydroxychloroquine), anti-viral agents, and antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, erythromycin, penicillin, mithramycin, and anthramycin (AMC)).

**[00324]** In a specific embodiment, the present invention provides a method comprising administering a formulation comprising one or more humanized anti-IL-9 antibodies to a subject, preferably a human subject, for preventing, treating, managing, or ameliorating a respiratory condition or one or more symptoms thereof. In one embodiment, the invention encompasses a method of preventing, treating, managing, or ameliorating a respiratory disorder or one or more symptoms thereof (e.g., an allergy, wheezing, and asthma), said method comprising administering to a subject in need thereof a dose of a prophylactically or

therapeutically effective amount of a formulation comprising one or more of humanized anti-IL-9 antibodies. In another embodiment, the invention provides a method of preventing, treating, managing, or ameliorating a respiratory infection or one or more symptoms thereof, said method comprising administering a prophylactically or therapeutic effective amount of one or more humanized anti-IL-9 antibodies.

**[00325]** In a specific embodiment, the present invention provides a method comprising administering a formulation of one or more humanized anti-EphA2 antibodies to a subject, preferably a human subject, for preventing, treating, managing, or ameliorating a hyperproliferative cell disease or one or more symptoms thereof. In one embodiment, one or more humanized anti-EphA2 antibodies are administered alone or in combination with other agents to a subject to prevent, treat, manage, or ameliorate cancer or one or more symptoms thereof (see, e.g., U.S. application Ser. No. 10/436,782, which is incorporated herein by reference in its entirety). In another embodiment, one or more humanized anti-EphA2 antibodies are administered alone or in combination with other agents to a subject to prevent, treat, manage, or ameliorate a disorder involving non-neoplastic hyperproliferative cells, in particular hyperproliferative epithelial and endothelial cells, or one or symptoms thereof (see e.g., U.S. Application Ser. No. 60/462,024, which is incorporated herein by reference in its entirety). In yet another embodiment, one or more humanized anti-EphA2 antibodies are used for diagnostic or screening purposes.

**[00326]** The formulations comprising antibodies and compositions of the invention can be used directly against a particular antigen. In some embodiments, the antibodies and compositions of the invention belong to a subclass or isotype that is capable of mediating the lysis of cells to which the antibody binds. In a specific embodiment, the antibodies of the invention belong to a subclass or isotype that, upon complexing with cell surface proteins, activates serum complement and/or mediates antibody dependent cellular cytotoxicity (ADCC) by activating effector cells such as natural killer cells or macrophages.

**[00327]** The biological activities of antibodies are known to be determined, to a large extent, by the constant domains or Fc region of the antibody molecule (Umanue and Benacerraf, Textbook of Immunology, 2nd Edition, Williams & Wilkins, p. 218 (1984)). This includes their ability to activate complement and to mediate antibody-dependent cellular cytotoxicity (ADCC) as effected by leukocytes. Antibodies of different classes and subclasses differ in this respect, as do antibodies from the same subclass but different species; according to the present invention, antibodies of those classes having the desired biological activity are prepared. Preparation of

these antibodies involves the selection of antibody constant domains and their incorporation in the humanized antibody by known technique. For example, mouse immunoglobulins of the IgG3 and IgG2a class are capable of activating serum complement upon binding to the target cells which express the cognate antigen, and therefore humanized antibodies which incorporate IgG3 and IgG2a effector functions are desirable for certain therapeutic applications.

[00328] In some embodiments, formulations of the invention comprising antibodies and compositions are useful in passively immunizing patients.

[00329] The formulations of the invention comprising antibodies and compositions can also be used in diagnostic assays either in vivo or in vitro for detection/identification of the expression of an antigen in a subject or a biological sample (*e.g.*, cells or tissues). Non-limiting examples of using an antibody, or a composition comprising an antibody in a diagnostic assay are given in U.S. Pat. Nos. 6,392,020; 6,156,498; 6,136,526; 6,048,528; 6,015,555; 5,833,988; 5,811,310; 8,565,114; 5,604,126; 5,484,704; 5,346,687; 5,318,892; 5,273,743; 5,182,107; 5,122,447; 5,080,883; 5,057,313; 4,910,133; 4,816,402; 4,742,000; 4,724,213; 4,724,212; 4,624,846; 4,623,627; 4,618,486; 4,176,174 (all of which are incorporated herein by reference). Suitable diagnostic assays for the antigen and its antibodies depend on the particular antibody used. Non-limiting examples are an ELISA, sandwich assay, and steric inhibition assays. For in vivo diagnostic assays using the antibodies of the invention, the antibodies may be conjugated to a label that can be detected by imaging techniques, such as X-ray, computed tomography (CT), ultrasound, or magnetic resonance imaging (MRI). The antibodies of the invention can also be used for the affinity purification of the antigen from recombinant cell culture or natural sources.

#### **5.5.1 Prophylactic and Therapeutic Use of Formulations of Antibodies against RSV infections**

[00330] The present invention provides antibody-based therapies which involve administering antibodies of the invention to a subject, preferably a human, for preventing, treating, or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). Prophylactic and therapeutic agents of the invention include, but are not limited to, antibodies (including analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies (including analogs and derivatives thereof and anti-idiotypic antibodies as described herein). Antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.



**[00331]** Formulations of the present invention comprising antibodies that function as antagonists of a RSV infection can be administered to a subject, preferably a human, to treat, prevent or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). For example, antibodies which disrupt or prevent the interaction between a RSV antigen and its host cell receptor may be administered to subject, preferably a human, to treat, prevent or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof).

**[00332]** In a specific embodiment, an antibody prevents or inhibits RSV from binding to its host cell receptor by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV binding to its host cell receptor in the absence of said antibodies or in the presence of a negative control in an assay known to one of skill in the art or described herein. In another embodiment, a combination of antibodies prevent or inhibit RSV from binding to its host cell receptor by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV binding to its host cell receptor in the absence of said antibodies or in the presence of a negative control in an assay known to one of skill in the art or described herein.

**[00333]** In a specific embodiment, an antibody prevents or inhibits RSV-induced fusion by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV-induced fusion in the absence of said antibodies or in the presence of a negative control in an assay known to one of skill in the art or described herein. In another embodiment, a combination of antibodies prevent or inhibit RSV-induced fusion by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV-induced fusion in

the absence of said antibodies or in the presence of a negative control in an assay known to one of skill in the art or described herein.

**[00334]** In a specific embodiment, an antibody prevents or inhibits RSV-induced fusion after viral attachment to cells by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV-induced fusion after viral attachment to cells in the absence of said antibodies or in the presence of a negative control in an assay known to one of skill in the art or described herein. In another embodiment, a combination of antibodies prevent or inhibit RSV-induced fusion after viral attachment to cells by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV-induced fusion after viral attachment to cells in the absence of said antibodies or in the presence of a negative control in an assay known to one of skill in the art or described herein.

**[00335]** Antibodies which do not prevent RSV from binding its host cell receptor but inhibit or downregulate RSV replication can also be administered to a subject to treat, prevent or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). The ability of an antibody to inhibit or downregulate RSV replication may be determined by techniques described herein or otherwise known in the art. For example, the inhibition or downregulation of RSV replication can be determined by detecting the RSV titer in the lungs of a subject, preferably a human. In further embodiments, the inhibition or downregulation of RSV replication can be determined by detecting the amount of RSV in the nasal passages or in the middle ear by methods known in the art (e.g., Northern blot analysis, RT-PCR, Western Blot analysis, etc.).

**[00336]** In some embodiments, a formulations of the present invention comprises an antibody that results in reduction of about 1-fold, about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 8-fold, about 10-fold, about 15-fold, about 20-fold, about 25-fold, about 30-fold, about 35-fold, about 40-fold, about 45-fold, about 50-fold, about 55-fold, about 60-fold, about 65-fold, about 70-fold, about 75-fold, about 80-fold, about 85-fold, about 90-fold, about 95-fold, about 100-fold, about 105 fold, about 110-fold, about 115-fold, about 120 fold, about 125-fold or higher in RSV titer in the lung. The fold-reduction in RSV titer may

be as compared to a negative control (such as placebo), as compared to another treatment (including, but not limited to treatment with palivizumab), or as compared to the titer in the patient prior to antibody administration.

**[00337]** In a specific embodiment, formulation of the present invention comprises an antibody that inhibits or downregulates RSV replication by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV replication in absence of said antibodies or in the presence of a negative control in an assay known in the art or described herein. In another embodiment, a combination of antibodies inhibit or downregulate RSV replication by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV replication in absence of said antibodies or in the presence of a negative control in an assay known in the art or described herein.

**[00338]** In some embodiments, formulation of the present invention comprises an antibody that results in reduction of about 1-fold, about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 8-fold, about 10-fold, about 15-fold, about 20-fold, about 25-fold, about 30-fold, about 35-fold, about 40-fold, about 45-fold, about 50-fold, about 55-fold, about 60-fold, about 65-fold, about 70-fold, about 75-fold, about 80-fold, about 85-fold, about 90-fold, about 95-fold, about 100-fold, about 105 fold, about 110-fold, about 115-fold, about 120 fold, about 125-fold or higher in RSV titer in the upper respiratory tract. The fold-reduction in RSV titer may be as compared to a negative control (such as placebo), as compared to another treatment (including, but not limited to treatment with palivizumab), or as compared to the titer in the patient prior to antibody administration.

**[00339]** In other embodiments, formulation of the present invention comprises an antibody that results in reduction of about 1-fold, about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 8-fold, about 10-fold, about 15-fold, about 20-fold, about 25-fold, about 30-fold, about 35-fold, about 40-fold, about 45-fold, about 50-fold, about 55-fold, about 60-fold, about 65-fold, about 70-fold, about 75-fold, about 80-fold, about 85-fold, about 90-fold, about 95-fold, about 100-fold, about 105 fold, about 110-fold, about 115-fold, about 120 fold, about 125-fold or higher in RSV titer in the lower respiratory tract. The fold-reduction in RSV titer may be as compared to a negative control (such as placebo), as compared to another

treatment (including, but not limited to treatment with palivizumab), or as compared to the titer in the patient prior to antibody administration.

**[00340]** One or more antibodies in connection with the present invention that immunospecifically bind to one or more RSV antigens may be used locally or systemically in the body as a prophylactic or therapeutic agent. The antibodies may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), which, for example, serve to increase the number or activity of effector cells which interact with the antibodies. The antibodies may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), which, for example, serve to increase the immune response. The antibodies may also be advantageously utilized in combination with one or more drugs used to treat RSV infection such as, for example anti-viral agents. Antibodies of the invention may be used in combination with one or more of the following drugs: NIH-351 (Gemini Technologies), recombinant RSV vaccine (Aviron), RSVf-2 (Intracel), F-50042 (Pierre Fabre), T-786 (Trimeris), VP-36676 (ViroPharma), RFI-641 (American Home Products), VP-14637 (ViroPharma), PFP-1 and PFP-2 (American Home Products), RSV vaccine (Avant Immunotherapeutics), and F-50077 (Pierre Fabre). In a specific embodiment, an effective amount of an antibody and an effective amount of another therapy is used.

**[00341]** The formulations of the invention comprising antibodies may be administered alone or in combination with other types of therapies (*e.g.*, hormonal therapy, immunotherapy, and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human or humanized antibodies, derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

**[00342]** In specific embodiments, an antibody is administered in combination with one or more anti-IL-9 antibodies (such as those disclosed in U.S. Publication No. 2005/0002934) either alone or in combination with one or more antibodies of the invention and/or other types of therapies or other agents (*e.g.*, hormone therapy, immunotherapy, and anti-inflammatory agents, such as those disclosed in U.S. Publication No. 2005/0002934, which is herein incorporated by reference in its entirety).

**[00343]** It is preferred to use high affinity and/or potent *in vivo* inhibiting antibodies and/or neutralizing antibodies that immunospecifically bind to a RSV antigen, for both immunoassays directed to RSV, and the prevention, management or treatment of an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). It is also preferred to use polynucleotides encoding high affinity and/or potent *in vivo* inhibiting antibodies and/or neutralizing antibodies that immunospecifically bind to a RSV antigen, for both immunoassays directed to RSV and therapy for an upper and/or lower respiratory tract RSV infection, otitis media (stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). Such antibodies will preferably have an affinity for the RSV F glycoprotein and/or fragments of the F glycoprotein.

**[00344]** The methods of the invention comprise the administration of one or more antibodies to patients suffering from or expected to suffer from (*e.g.*, patients with a genetic predisposition for or patients that have previously suffered from) an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). Such patients may have been previously treated or are currently being treated for the infection, otitis media, or a respiratory condition, *e.g.*, with a therapy other than an antibody of the invention. In one embodiment, the methods of the invention comprise the administration of one or more antibodies to patients that are immunocompromised or immunosuppressed. In a certain embodiment, an antibody administered to patients that are immunocompromised or immunosuppressed. In another embodiment, an antibody is administered to a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, or to a human who has had a bone marrow transplant to treat, prevent or ameliorate one or more symptoms associated with an upper and/or lower respiratory tract RSV infection or otitis media (preferably, stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). In another embodiment, a formulation of the invention comprising an antibody is administered to a human infant, preferably a human infant born prematurely or a human infant at risk of hospitalization for RSV infection to treat, prevent or ameliorate one or more symptoms associated with an upper and/or

lower respiratory tract RSV infection or otitis media. In yet another embodiment, a formulation of the invention comprising an antibody is administered to the elderly or people in group homes (e.g., nursing homes or rehabilitation centers). In accordance with the invention, a formulation of the invention comprising an antibody may be used as any line of therapy, including, but not limited to, a first, second, third and fourth line of therapy, including, but not limited to, a first, second, third and fourth line of therapy. Further, in accordance with the invention, a formulation of the invention comprising an antibody can be used before any adverse effects or intolerance of the therapies other than an antibody occurs. The invention encompasses methods for administering one or more antibodies to prevent the onset or recurrence of an upper and/or lower respiratory tract RSV infection or otitis media.

[00345] In one embodiment, the invention also provides methods of treatment, management, prevention and/or amelioration of an upper and/or lower respiratory tract RSV infection (preferably stemming from, caused by, or associated with a RSV infection), otitis media or a symptom or respiratory condition related thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) as alternatives to current therapies. In a specific embodiment, the current therapy has proven or may prove too toxic (*i.e.*, results in unacceptable or unbearable side effects) for the patient. In another embodiment, an antibody decreases the side effects as compared to the current therapy. In another embodiment, the patient has proven refractory to a current therapy. In such embodiments, the invention provides for the administration of one or more antibodies of the invention without any other anti-infection therapies. In certain embodiments, one or more antibodies can be administered to a patient in need thereof instead of another therapy to treat an upper and/or lower respiratory tract RSV infection, otitis media or a symptom or respiratory condition related thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). In one embodiment, the invention provides methods of treating, managing, preventing and/or ameliorating an active upper and/or lower respiratory tract RSV infection, otitis media or a symptom or respiratory condition related thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof).

[00346] The present invention also encompasses methods for administering one or more antibodies to treat or ameliorate symptoms of an upper and/or lower respiratory tract RSV infection or otitis media in patients that are or have become refractory to therapies other than the antibodies. The determination whether the infection is refractory can be made either *in vivo* or *in vitro* by any method known in the art for assaying the effectiveness of a therapy on affected

cells in the infection, particularly epithelial cells, or in patients that are or have become refractory to therapies other than antibodies of the invention.

**[00347]** In certain embodiments, an effective amount of one or more antibodies in the formulation of the invention is administered in combination with one or more supportive measures to a subject in need thereof to prevent, manage, treat, and/or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). Non-limiting examples of supportive measures include humidification of the air by an ultrasonic nebulizer, aerolized racemic epinephrine, oral dexamethasone, intravenous fluids, intubation, fever reducers (*e.g.*, ibuprofen, acetaminophen), and antibiotic and/or anti-fungal therapy (*i.e.*, to prevent or treat secondary bacterial and/or fungal infections).

**[00348]** In a specific embodiment, the invention provides methods for preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by, or associated with a RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof), said methods comprising administering to a subject in need thereof an effective amount of one or more antibodies of the invention alone or in combination with one or more anti-viral agents such as, but not limited to, amantadine, rimantadine, oseltamivir, zanamivir, ribavirin, RSV-IVIG (*i.e.*, intravenous immune globulin infusion) (RESPIGAM™), EphA2/EphrinA1 Modulators, and/or an anti-IL-9 antibody (see, *e.g.*, U.S. Publication No. 2005/0002934).

**[00349]** In a specific embodiment, the invention provides methods for preventing, treating, managing, and/or ameliorating one or more secondary responses to a primary viral infection, said methods comprising administering an effective amount of one or more antibodies alone or in combination with an effective amount of other therapies (*e.g.*, other prophylactic or therapeutic agents). Examples of secondary responses to a primary viral infection include, but are not limited to, asthma-like responsiveness to mucosal stimuli, elevated total respiratory resistance, increased susceptibility to secondary viral, bacterial, and fungal infections, and development of conditions such as, but not limited to, bronchiolitis, pneumonia, croup, and febrile bronchitis.

[00350] In a specific embodiment, the invention provides methods of preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD, or a combination thereof), said methods comprising administering to a subject in need thereof an effective amount of one or more antibodies in combination with an effective amount of an EphA2/EphrinA1 Modulator (U.S. Provisional Appn. Serial No. 60/622,489, filed October 27, 2004, entitled "Use of Modulators of EphA2 and EphrinA1 for the Treatment and Prevention of Infections", which is incorporated by reference herein in its entirety). In another specific embodiment, the invention provides methods for preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD, or a combination thereof), said methods comprising administering to a subject in need thereof an effective amount of one or more antibodies in combination with an effective amount of siplizumab (MedImmune, Inc., International Pub. No. WO 02/069904, which is incorporated herein by reference in its entirety). In another embodiment, the invention provides methods of preventing, treating, managing and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD, or a combination thereof), said methods comprising administering to a subject in need thereof an effective amount of one or more antibodies in combination with an effective amount of one or more anti-IL-9 antibodies, such as those disclosed in U.S. Publication No. 2005/0002934, which is incorporated herein by reference in its entirety. In yet another embodiment, the invention provides methods for preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD, or a combination thereof), said methods comprising administering to a subject in need thereof an effective amount of one or more antibodies of the invention in combination with an effective amount of two or more of the following: EphA2/EphrinA1 Modulators, an anti-IL-9 antibody and/or siplizumab.



[00351] The formulations of the invention, comprising antibodies, compositions, or combination therapies of the invention may be used as any line of therapy, including but not limited to, the first, second, third, fourth, or fifth line of therapy, to prevent, treat, and/or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD, or a combination thereof). The invention also includes methods of preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) in a patient undergoing therapies for other diseases or disorders (*e.g.*, non-RSV infections). The invention encompasses methods of preventing, managing, treating, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD, or a combination thereof) in a patient before any adverse effects or intolerance to therapies other than antibodies of the invention develops.

[00352] The invention also encompasses methods of preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) in refractory patients. In certain embodiments, a patient with an upper and/or lower respiratory tract RSV infection, is refractory to a therapy when the infection has not significantly been eradicated and/or the symptoms have not been significantly alleviated. The determination of whether a patient is refractory can be made either *in vivo* or *in vitro* by any method known in the art for assaying the effectiveness of a therapy for infections, using art-accepted meanings of "refractory" in such a context. In various embodiments, a patient with an upper and/or lower respiratory tract RSV infection is refractory when viral replication has not decreased or has increased. The invention also encompasses methods of preventing the onset or reoccurrence of an upper and/or lower respiratory tract RSV infection or otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper

and/or lower respiratory tract RSV infection) in patients at risk of developing such infections or otitis media.

**[00353]** The invention also encompasses methods of preventing, managing, treating, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) in patients who are susceptible to adverse reactions to conventional therapies. The invention further encompasses methods for preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection) or otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) for which no anti-viral therapy is available.

**[00354]** The invention encompasses methods for preventing, treating, managing, and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) in a patient who has proven refractory to therapies other than antibodies of the invention but are no longer on these therapies. In certain embodiments, the patients being treated in accordance with the methods of this invention are patients already being treated with antibiotics, anti-virals, anti-fungals, or other biological therapy/immunotherapy. Among these patients are refractory patients, patients who are too young for conventional therapies, and patients with reoccurring upper and/or lower respiratory tract RSV infections or otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) despite treatment with existing therapies.

**[00355]** The present invention encompasses methods for preventing, treating and/or ameliorating a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection), or a symptom or respiratory condition

relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) as an alternative to other conventional therapies. In specific embodiments, the patient being or treated in accordance with the methods of the invention is refractory to other therapies or is susceptible to adverse reactions from such therapies. The patient may be a person with a suppressed immune system (*e.g.*, post-operative patients, chemotherapy patients, and patients with immunodeficiency disease), a person with impaired renal or liver function, the elderly, children, infants, infants born prematurely, persons with neuropsychiatric disorders or those who take psychotropic drugs, persons with histories of seizures, or persons on medication that would negatively interact with conventional agents used to prevent, treat, and/or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof).

[00356] The dosage amounts and frequencies of administration provided herein are encompassed by the terms “effective amount”, “therapeutically effective” and “prophylactically” effective. The dosage and frequency further will typically vary according to factors specific for each patient depending on the specific therapeutic or prophylactic agents administered, the severity and type of infection, the route of administration, as well as age, body weight, response, and the past medical history of the patient. Suitable regimens can be selected by one skilled in the art by considering such factors and by following, for example, dosages reported in the literature and recommended in the Physician’s Desk Reference (58<sup>th</sup> ed., 2004). See Section 5.3 for specific dosage amounts and frequencies of administration of the prophylactic and therapeutic agents provided by the invention.

## **5.6 Methods of Administration of Antibodies**

[00357] The a specific embodiment, the invention provides methods of treatment, prophylaxis, and amelioration of an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) by administering to a subject of an effective amount of antibody, or pharmaceutical composition comprising the formulation comprising an antibody of the invention. In a preferred aspect, an antibody is substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject administered a therapy is preferably a mammal such as non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats etc.) and a primate (*e.g.*,

monkey such as a cynomolgous monkey and a human). In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a human infant or a human infant born prematurely. In another embodiment, the subject is a human with an upper and/or lower respiratory tract RSV infection, otitis media stemming from, caused by or associated with a RSV infection, cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, a human who has had a bone marrow transplant, or an elderly human.

**[00358]** Various delivery systems are known and can be used to administer a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), including, but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of administering a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), or pharmaceutical composition include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal and oral routes). In a specific embodiment, a prophylactic or therapeutic agent (*e.g.*, an antibody of the present invention), or a pharmaceutical composition is administered intramuscularly, intravenously, or subcutaneously. The prophylactic or therapeutic agents, or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Patent Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety. In a specific embodiment, an antibody, or formulation of the invention is administered using Alkermes AIR™ pulmonary drug delivery technology (Alkermes, Inc., Cambridge, MA).

**[00359]** In a specific embodiment, it may be desirable to administer a prophylactic or therapeutic agent, or a pharmaceutical formulation of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous

material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering an antibody of the invention, care must be taken to use materials to which the antibody does not absorb.

**[00360]** In another embodiment, a prophylactic or therapeutic agent, or a formulation of the invention can be delivered in a vesicle, in particular a liposome (see Langer, 1990, *Science* 249:1527-1533; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

**[00361]** In another embodiment, a prophylactic or therapeutic agent, or a formulation of the invention can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:20; Buchwald et al., 1980, *Surgery* 88:507; Saudek et al., 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of a prophylactic or therapeutic agent (*e.g.*, an antibodies of the invention) or a formulation of the invention (see *e.g.*, *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; see also Levy et al., 1985, *Science* 228:190; During et al., 1989, *Ann. Neurol.* 25:351; Howard et al., 1989, *J. Neurosurg.* 71:105); U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a controlled or sustained release system can be placed in proximity of the therapeutic target, *i.e.*, the nasal passages or lungs, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

**[00362]** Controlled release systems are discussed in the review by Langer (1990, Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the invention. See, *e.g.*, U.S. Patent No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning et al., 1996, "Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179- 189, Song et al., 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek et al., 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam et al., 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in their entirety.

**[00363]** In a specific embodiment, a formulation of the invention comprises one, two or more antibodies described, *infra*. In another embodiment, a formulation of the invention comprises one, two or more antibodies described, *infra*, and a prophylactic or therapeutic agent other than an said antibody. In a specific embodiment, the agents are known to be useful for or have been or are currently used for the prevention, treatment or ameliorating of a RSV infection (preferably, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). In addition to prophylactic or therapeutic agents, the compositions of the invention may also comprise a carrier.

**[00364]** The formulations of the invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions (*e.g.*, compositions that are suitable for administration to a subject or patient) which can be used in the preparation of unit dosage forms. In a preferred embodiment, a composition of the invention is a pharmaceutical composition. Such compositions comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (*e.g.*, an antibody of the invention or other prophylactic or therapeutic agent), and a pharmaceutically acceptable carrier. Preferably, the pharmaceutical compositions are formulated to be suitable for the route of administration to a subject.

**[00365]** In a specific embodiment, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant (*e.g.*, Freund’s adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in “Remington’s Pharmaceutical Sciences” by E.W. Martin. Such compositions will contain a prophylactically or therapeutically effective amount of the antibody, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

**[00366]** In a preferred embodiment, the formulations are manufactured in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection.

**[00367]** Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or

saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

**[00368]** The invention also provides that the formulation is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of antibody. In one embodiment, the formulation of the invention comprising an antibody is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.*, with water or saline to the appropriate concentration for administration to a subject. In one embodiment, the formulation of the invention comprising an antibody is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 3 mg, more preferably at least 5 mg, at least 10 mg, at least 15 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 60 mg, or at least 75 mg. The lyophilized formulation of the invention comprising an antibody should be stored at between 2 and 8° C in its original container and the antibody should be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, a formulation of the invention comprising an antibody is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody. Preferably, the liquid form of the formulation of the invention comprising an antibody is supplied in a hermetically sealed container at least 1 mg/ml, more preferably at least 2.5 mg/ml, at least 3 mg/ml, at least 5 mg/ml, at least 8 mg/ml, at least 10 mg/ml, at least 15 mg/ml, at least 25 mg/ml, at least 30 mg/ml, or at least 60 mg/ml.

**[00369]** The formulation of the invention comprising antibodies can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

**[00370]** The amount of a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), or a composition of the invention which will be effective in the treatment, prevention or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) can be determined by standard clinical techniques. For example, the dosage of a prophylactic or therapeutic agent, or a composition which will be effective in the treatment, prevention or



amelioration of an upper and/or lower respiratory tract RSV infection or one or more symptoms thereof can be determined by administering the composition to a cotton rat, measuring the RSV titer after challenging the cotton rat with  $10^5$  pfu of RSV and comparing the RSV titer to that obtain for a cotton rat not administered the prophylactic or therapeutic agent, or the composition. Accordingly, a dosage that results in a 2 log decrease or a 99% reduction in RSV titer in the cotton rat challenged with  $10^5$  pfu of RSV relative to the cotton rat challenged with  $10^5$  pfu of RSV but not administered the prophylactic or therapeutic agent, or the composition is the dosage of the composition that can be administered to a human for the treatment, prevention or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof.

[00371] The dosage of a composition which will be effective in the treatment, prevention or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof can be determined by administering the composition to an animal model (*e.g.*, a cotton rat or monkey) and measuring the serum titer, lung concentration or nasal turbinate and/or nasal secretion concentration of an antibody that immunospecifically bind to a RSV antigen. Accordingly, a dosage of an antibody or a composition that results in a serum titer of at least 1  $\mu\text{g/ml}$ , preferably 2  $\mu\text{g/ml}$ , 5  $\mu\text{g/ml}$ , 10  $\mu\text{g/ml}$ , 15  $\mu\text{g/ml}$ , 20  $\mu\text{g/ml}$ , 25  $\mu\text{g/ml}$ , at least 30  $\mu\text{g/ml}$ , at least 35  $\mu\text{g/ml}$ , at least 40  $\mu\text{g/ml}$ , at least 50  $\mu\text{g/ml}$ , at least 75  $\mu\text{g/ml}$ , at least 100  $\mu\text{g/ml}$ , at least 125  $\mu\text{g/ml}$ , at least 150  $\mu\text{g/ml}$ , at least 200  $\mu\text{g/ml}$ , at least 250  $\mu\text{g/ml}$ , at least 300  $\mu\text{g/ml}$ , at least 350  $\mu\text{g/ml}$ , at least 400  $\mu\text{g/ml}$ , or at least 450  $\mu\text{g/ml}$  can be administered to a human for the treatment, prevention or amelioration of an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges.

[00372] The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the upper and/or lower respiratory tract RSV infection or otitis media, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model (*e.g.*, the cotton rat or Cynomolgous monkey) test systems.

**[00373]** For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. In some embodiments, the dosage administered to the patient is about 3 mg/kg to about 60 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 15 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (*e.g.*, into the nasal passages and/or lung) of the antibodies by modifications such as, for example, lipidation. In a preferred embodiment, the dosage of A4B4L1FR-S28R (motavizumab) or antigen-binding fragment thereof to be administered to is 60 mg/kg, 50 mg/kg, 40 mg/kg, 30 mg/kg, 15 mg/kg, 10 mg/kg, 5 mg/kg, 3 mg/kg, or 2 mg/kg of the patient's body weight.

**[00374]** In a specific embodiment, formulations of the invention comprising antibodies or compositions comprising antibodies are administered once a month just prior to or during the RSV season. In another embodiment, formulation of the invention comprising an antibody, or compositions comprising antibodies produced in accordance with the methods of the invention are administered every two months just prior to or during the RSV season. In yet another embodiment, antibodies, or compositions comprising antibodies are administered once just prior to or during the RSV season. The term "RSV season" refers to the season when RSV infection is most likely to occur. Typically, the RSV season in the northern hemisphere commences in November and lasts through April. Preferably, the antibody comprises the VH and VL domain of A4B4L1FR-S28R (motavizumab) (Figure 13) or an antigen-binding fragment thereof.

**[00375]** In one embodiment, approximately 60 mg/kg or less, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of an antibody the invention is administered 5 times, 4 times, 3 times, 2 times or 1 time during a RSV season to a subject, preferably a human. In some embodiments, the antibody is administered about 1-12 times during the RSV season to a subject, wherein the doses may be administered as necessary, *e.g.*, weekly, biweekly, monthly, bimonthly, trimonthly, *etc.*, as determined by a physician. In some embodiments, a lower dose (*e.g.*, 5-15 mg/kg) can be administered more frequently (*e.g.*, 3-6 times) during a RSV season. In other embodiments, a higher dose (*e.g.*, 30-60 mg/kg) can be administered less frequently

(*e.g.*, 1-3 times) during a RSV season. However, as will be apparent to those in the art, other dosing amounts and schedules are easily determinable and within the scope of the invention.

**[00376]** In one embodiment, approximately 60 mg/kg or less, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of an antibody is administered to monthly five times during a RSV season to a subject, preferably a human, intramuscularly. In another embodiment, approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of an antibody the invention is administered monthly three times during a RSV season to a subject, preferably a human, intramuscularly. In yet another embodiment, approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of an antibody is administered monthly one to two times during a RSV season to a subject, preferably a human, intramuscularly. Preferably, the antibody comprises the VH and VL domain of A4B4L1FR-S28R (motavizumab) (Figure 13) or an antigen-binding fragment thereof.

**[00377]** In a specific embodiment, approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of an antibody in a sustained release formulation is administered to a subject, preferably a human, to prevent, treat or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof. In another specific embodiment, an approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less bolus of an antibody the invention not in a sustained release formulation is administered to a subject, preferably a human, to prevent, treat or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof and after a

certain period of time approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of the invention in a sustained release is administered to said subject intramuscularly two, three or four times during a RSV season. In accordance with this embodiment, a certain period of time can be 1 to 5 days, a week, two weeks, or a month. In another embodiment, approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of an antibody in a sustained release formulation is administered to a subject, preferably a human, intramuscularly two, three or four times during a RSV season to prevent, treat or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof. Preferably, the antibody is A4B4L1FR-S28 or an antigen-binding fragment thereof.

**[00378]** In another embodiment, approximately 60 mg/kg, approximately 45 mg/kg or less, approximately 30 mg/kg or less, approximately 15 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 3 mg/kg or less, approximately 2 mg/kg or less, or approximately 1.5 mg/kg or less of one or more antibodies of the invention is administered intranasally to a subject to prevent, treat or ameliorate an upper and/or lower respiratory tract RSV infection, otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection) or one or more symptoms thereof. Preferably, the antibody is A4B4L1FR-S28 or an antigen-binding fragment thereof. Preferably, the antibody is A4B4L1FR-S28 or an antigen-binding fragment thereof.

**[00379]** In one embodiment, a single dose of the formulation of the invention comprising an antibody (preferably motavizumab) is administered to a patient (preferably a human), wherein the dose is selected from the group consisting of about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, or about 75 mg/kg.

**[00380]** In some embodiments, a single dose of a formulation of the invention comprising an antibody (preferably motavizumab) is administered to a patient (preferably a human) two, three, four, five, six, seven, eight, nine, ten, eleven, twelve times, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty five, or twenty six at bi-weekly (*e.g.*, about 14 day) intervals over the course of a year (or alternatively over the course of a RSV season), wherein the dose is selected from the group consisting of about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, or a combination thereof (*i.e.*, each dose monthly dose may or may not be identical).

**[00381]** In another embodiment, a single dose of a formulation of the invention comprising an antibody (preferably motavizumab) is administered to patient (preferably a human) two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve times at about monthly (*e.g.*, about 30 day) intervals over the course of a year (or alternatively over the course of a RSV season), wherein the dose is selected from the group consisting of about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, or a combination thereof (*i.e.*, each dose monthly dose may or may not be identical).

**[00382]** In one embodiment, a single dose of a formulation of the invention comprising an antibody (preferably motavizumab) is administered to a patient (preferably a human) two, three, four, five, or six times at about bi-monthly (*e.g.*, about 60 day) intervals over the course of a year (or alternatively over the course of a RSV season), wherein the dose is selected from the group consisting of about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, or a combination thereof (*i.e.*, each bi-monthly dose may or may not be identical).

**[00383]** In some embodiments, a single dose of a formulation of the invention comprising an antibody (preferably motavizumab) is administered to a patient (preferably a human) two, three, or four times at about tri-monthly (*e.g.*, about 120 day) intervals over the course of a year (or alternatively over the course of a RSV season), wherein the dose is selected from the group

consisting of about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, or a combination thereof (*i.e.*, each tri-monthly dose may or may not be identical).

**[00384]** In certain embodiments, the route of administration for a dose of a formulation of the invention comprising an antibody to a patient is intramuscular, intravenous, or a combination thereof (*i.e.*, each dose may or may not be administered by an identical route of administration). In some embodiments, an antibody of the invention may be administered via multiple routes of administration simultaneously or subsequently to other doses of the same or a different antibody of the invention.

### **5.7 Biological Activity**

**[00385]** Formulations of the invention comprising antibodies may be characterized in a variety of ways. In particular, antibodies may be assayed for the ability to immunospecifically bind to a RSV antigen. Such an assay may be performed in solution (*e.g.*, Houghten, 1992, *Bio/Techniques* 13:412-421), on beads (Lam, 1991, *Nature* 354:82-84), on chips (Fodor, 1993, *Nature* 364:555-556), on bacteria (U.S. Patent No. 5,223,409), on spores (U.S. Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (Cull et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla et al., 1990, *Proc. Natl. Acad. Sci. USA* 87:6378-6382; and Felici, 1991, *J. Mol. Biol.* 222:301-310) (each of these references is incorporated herein in its entirety by reference). Antibodies that have been identified to immunospecifically bind to a RSV antigen (*e.g.*, a RSV F antigen) can then be assayed for their specificity and affinity for a RSV antigen.

**[00386]** Formulations of the invention comprising antibodies may be assayed for immunospecific binding to a RSV antigen and cross-reactivity with other antigens by any method known in the art. Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*,

Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

**[00387]** Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasyolol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

**[00388]** Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, incubating the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), incubating the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, incubating the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

**[00389]** ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

**[00390]** The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for a RSV antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, a RSV antigen is incubated with an antibody of the present invention conjugated to a labeled compound (*e.g.*,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

**[00391]** In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies to a RSV antigen. BIAcore kinetic analysis comprises analyzing the binding and dissociation of a RSV antigen from chips with immobilized antibodies on their surface.

**[00392]** Formulations of the invention comprising antibodies can also be assayed for their ability to inhibit the binding of RSV to its host cell receptor using techniques known to those of skill in the art. For example, cells expressing the receptor for RSV can be contacted with RSV in the presence or absence of an antibody and the ability of the antibody to inhibit RSV's binding can be measured by, for example, flow cytometry or a scintillation assay. RSV (*e.g.*, a RSV antigen such as F glycoprotein or G glycoprotein) or the antibody can be labeled with a



detectable compound such as a radioactive label (*e.g.*,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , and  $^{125}\text{I}$ ) or a fluorescent label (*e.g.*, fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, *o*-phthaldehyde and fluorescamine) to enable detection of an interaction between RSV and its host cell receptor. Alternatively, the ability of antibodies to inhibit RSV from binding to its receptor can be determined in cell-free assays. For example, RSV or a RSV antigen such as G glycoprotein can be contacted with an antibody and the ability of the antibody to inhibit RSV or the RSV antigen from binding to its host cell receptor can be determined. Preferably, the antibody is immobilized on a solid support and RSV or a RSV antigen is labeled with a detectable compound. Alternatively, RSV or a RSV antigen is immobilized on a solid support and the antibody is labeled with a detectable compound. RSV or a RSV antigen may be partially or completely purified (*e.g.*, partially or completely free of other polypeptides) or part of a cell lysate. Further, a RSV antigen may be a fusion protein comprising the RSV antigen and a domain such as glutathione S transferase. Alternatively, a RSV antigen can be biotinylated using techniques well known to those of skill in the art (*e.g.*, biotinylation kit, Pierce Chemicals; Rockford, IL).

**[00393]** Formulations of the invention comprising antibodies can also be assayed for their ability to inhibit or downregulate RSV replication using techniques known to those of skill in the art. For example, RSV replication can be assayed by a plaque assay such as described, *e.g.*, by Johnson et al., 1997, Journal of Infectious Diseases 176:1215-1224. The antibodies of the invention can also be assayed for their ability to inhibit or downregulate the expression of RSV polypeptides. Techniques known to those of skill in the art, including, but not limited to, Western blot analysis, Northern blot analysis, and RT-PCR can be used to measure the expression of RSV polypeptides. Further, the antibodies of the invention can be assayed for their ability to prevent the formation of syncytia.

**[00394]** Formulations of the invention comprising antibodies are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a subject tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a RSV infection (*e.g.*, respiratory epithelial cells), to determine if an antibody or composition

of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans. In a specific embodiment, cotton rats are administered an antibody the invention, or a composition of the invention, challenged with  $10^5$  pfu of RSV, and four or more days later the rats are sacrificed and RSV titer and anti-RSV antibody serum titer is determined. Further, in accordance with this embodiment, the tissues (*e.g.*, the lung tissues) from the sacrificed rats can be examined for histological changes.

[00395] In accordance with the invention, clinical trials with human subjects need not be performed in order to demonstrate the prophylactic and/or therapeutic efficacy of antibodies of the invention. *In vitro* and animal model studies using the antibodies can be extrapolated to humans and are sufficient for demonstrating the prophylactic and/or therapeutic utility of said antibodies.

[00396] Formulations of the invention comprising antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.

[00397] Efficacy in treating or preventing an upper and/or lower respiratory tract RSV infection may be demonstrated by determining the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, to reduce the incidence of an upper and/or lower respiratory tract RSV infection, to prevent or reduce the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection, or to prevent, ameliorate or alleviate one or more symptoms associated with an upper and/or lower respiratory tract RSV infection. Efficacy in treating or preventing otitis media may be demonstrated by determining the ability of an antibody or composition of the invention to reduce the incidence of otitis media, to reduce the duration of otitis media, to prevent or reduce the progression of an upper and/or lower respiratory tract RSV infection to otitis media, or to ameliorate one or more symptoms of otitis media. A therapy is considered therapeutic if there is, for example, a reduction in viral load, amelioration of one or more symptoms of an upper and/or lower respiratory tract RSV infection or otitis media, or a respiratory condition relating thereto (including, but not limited to asthma, wheezing, RAD or a combination thereof), a reduction in the duration of an upper and/or lower respiratory tract RSV infection or otitis media, a reduction in lower respiratory tract RSV infections, or a decrease in mortality and/or morbidity following administration of an antibody

or composition of the invention. Further, the treatment is considered therapeutic if there is an increase in the immune response following the administration of one or more antibodies which immunospecifically bind to one or more RSV antigens.

**[00398]** Formulations of the invention comprising antibodies or compositions of the invention can be tested *in vitro* and *in vivo* for the ability to induce the expression of cytokines such as IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , IL- $2$ , IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 and IL-15. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, an antibody or composition of the invention is tested for its ability to induce the expression of IFN- $\gamma$ .

**[00399]** Formulations of the invention comprising antibodies or compositions of the invention can be tested *in vitro* and *in vivo* for their ability to modulate the biological activity of immune cells, preferably human immune cells (*e.g.*, T-cells, B-cells, and Natural Killer cells). The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells, detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by  $^3\text{H}$  thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSAs).

**[00400]** Formulations of the invention comprising antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load in *in vitro*, *ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of a RSV infection (*i.e.*, an upper and/or lower

respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). Antibodies or compositions of the invention can also be tested for their ability to increase the survival period of humans suffering from a RSV infection (preferably, an upper and/or lower respiratory tract RSV infection) by at least 25%, preferably at least 50%, at least 60%, at least 75%, at least 85%, at least 95%, or at least 99%. Further, antibodies or compositions of the invention can be tested for their ability reduce the hospitalization period of humans suffering from a RSV infection (preferably, an upper and/or lower respiratory tract RSV infection) by at least 60%, preferably at least 75%, at least 85%, at least 95%, or at least 99%. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

#### **5.8 Diagnostic Uses of Antibodies for Detecting RSV Infections**

[00401] Labeled antibodies and derivatives and analogs thereof, which immunospecifically bind to a RSV antigen can be used for diagnostic purposes to detect, diagnose, or monitor an upper and/or lower respiratory tract RSV infection or otitis media (preferably, stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract RSV infection). The invention provides for the detection of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprising: (a) assaying the expression of a RSV antigen in cells or a tissue sample of a subject using one or more antibodies that immunospecifically bind to the RSV antigen; and (b) comparing the level of the RSV antigen with a control level, *e.g.*, levels in normal tissue samples not infected with RSV, whereby an increase in the assayed level of RSV antigen compared to the control level of the RSV antigen is indicative of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof).

[00402] The invention provides a diagnostic assay for diagnosing a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract

infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) comprising: (a) assaying for the level of a RSV antigen in cells or a tissue sample of an individual using one or more antibodies that immunospecifically bind to a RSV antigen; and (b) comparing the level of the RSV antigen with a control level, *e.g.*, levels in normal tissue samples not infected with RSV, whereby an increase in the assayed RSV antigen level compared to the control level of the RSV antigen is indicative of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). A more definitive diagnosis of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the RSV infection or otitis media.

**[00403]** Antibodies of the invention can be used to assay RSV antigen levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (*e.g.*, see Jalkanen et al., 1985, J. Cell. Biol. 101:976-985; and Jalkanen et al., 1987, J. Cell. Biol. 105:3087-3096). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{121}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[00404]** One aspect of the invention is the detection and diagnosis of a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof) in a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or

intraperitoneally) to a subject an effective amount of a labeled antibody that immunospecifically binds to a RSV antigen; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject (*e.g.*, the nasal passages, lungs, mouth and ears) where the RSV antigen is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody above the background level indicates that the subject has a RSV infection (*i.e.*, an upper and/or lower respiratory tract RSV infection), otitis media (preferably stemming from, caused by or associated with a RSV infection, such as an upper and/or lower respiratory tract infection), or a symptom or respiratory condition relating thereto (including, but not limited to, asthma, wheezing, RAD, or a combination thereof). Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[00405] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99</sup>Tc. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B.A. Rhodes, eds., Masson Publishing Inc. (1982).

[00406] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled antibody to preferentially concentrate at sites in the subject and for unbound labeled antibody to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[00407] In one embodiment, monitoring of an upper and/or lower respiratory tract RSV infection is carried out by repeating the method for diagnosing the upper and/or lower respiratory tract RSV infection, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[00408] Presence of the labeled molecule can be detected in the subject using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used.

Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[00409] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

### 5.9 Kits

[00410] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical formulation of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00411] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated RSV antigen as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with the RSV antigen. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a RSV antigen (*e.g.*, the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized RSV antigen. The RSV antigen provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above described kit includes a solid support to which RSV antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this

embodiment, binding of the antibody to the RSV antigen can be detected by binding of the said reporter-labeled antibody.

[00412]

## 6. EXAMPLES

[00413] The following examples are offered to illustrate this invention and not to be construed in any way as limiting the scope of this invention.

### 6.1 EXAMPLE: CHARACTERIZATION OF ANTIBODY FORMULATION FOR ANTIBODY FRAGMENTATION AND AGGREGATION

[00414] This example illustrates the characterization of an antibody formulation for antibody fragmentation and aggregation. Antibody A4B4L1FR-S28R is used in this example. As discussed in the sections above antibody A4B4L1FR-S28R is an IgG1 monoclonal antibody produced by recombinant DNA technology that specifically binds to an epitope in the A antigenic site of the fusion (F) protein of RSV. A4B4L1FR-S28R is a humanized antibody and consists of the CDR regions specific for the targeted antigen and the constant regions of a human  $\gamma 1$  heavy chain and  $\kappa$  light chain. The monoclonal antibody has two inter-chain disulfide bonds to link heavy and light chains, and another two inter-chain disulfide bonds at the hinge region. Unless otherwise indicated, all antibody samples in this example were formulated at a concentration of 100 mg/ml in 25 mM histidine-HCl, pH 6.0. Further storage conditions are reported in the section describing experimental results.

#### Materials and Methods

##### Size Exclusion Chromatography (SEC)

[00415] Size exclusion chromatography was performed to analyze the antibody formulation for the presence of antibody aggregates and fragments. The test samples were injected onto a size exclusion G3000 SW<sub>XL</sub> column (5  $\mu$ m, 300 Å, 7.8 x 300 mm, TosoHaas). The mobile phase was 0.1 M di-sodium phosphate, 0.1 M sodium sulphate and 0.05 % sodium azide (pH 6.7), running isocratically at a flow rate of 0.25 - 1.0 mL/min. Eluted protein was detected by UV absorbance at 280 nm and collected for further characterization. The relative amount of any protein species detected was reported as the area percent of the product peak as compared to the total area of all other detected peaks excluding the initial included volume peak. Peaks eluting earlier than the antibody monomer peak were recorded in the aggregate percentile, while peaks eluting later than the antibody monomer peak, but earlier than the buffer peak, were



recorded in the fragment percentile. The hydrodynamic radius and molecular weight of the individual peaks were obtained with a coupled multiangle light scattering detector.

#### **Analytical Ultracentrifugation (AUC)**

[00416] Analytical ultracentrifugation (AUC) was also used to characterize the antibody formulation. AUC is an orthogonal technique which determines the sedimentation coefficients (reported in Svedberg, S) of macromolecules in a liquid sample. Like SEC, AUC is capable of separating and detecting antibody fragments/aggregates from monomers and is further able to provide information on molecular mass. Compared to SEC, AUC eliminates the possibility of aggregate loss due to solid-phase interaction and is better able to resolve differing species of a given macromolecule.

[00417] Sedimentation velocity experiments were performed using a Beckman Optima XL-A analytical ultracentrifuge. Test samples were diluted to an antibody concentration of 0.5 mg/ml with reference buffer (20 mM citric acid, 100 mM NaCl, 1.5% mannitol, 50  $\mu$ M diethylenetriamine-pentaacetic acid, 0.02% Polysorbate 80, pH 6.0). 415  $\mu$ l of the diluted antibody sample and 412  $\mu$ l of the reference buffer were loaded into a 12 mm centrifuge cell in the sample and reference channels, respectively. Loaded cells were placed into an AN-50Ti analytical rotor and equilibrated to 25 °C. Samples were scanned at 280 nm with a rotor speed of 42000 rpm at full vacuum. A total of 80 scans for each cell were collected for analysis. The first scan for each sample was excluded to avoid artifacts caused by meniscus.

[00418] The data were analyzed using the  $c(s)$  method developed by Peter Shuck at N.I.H. and the SEDFIT (version 8.8) program with implemented  $c(s)$ . Using the  $c(s)$  method, raw data scans are directly fit to a Lamm function of S in order to derive a distribution of sedimentation coefficients. The parameters used for the fitting procedure were resolution, 400; confidence interval, 0.75; grid size, 1000; partial specific volume, 0.7245; buffer density, 1.000; and buffer viscosity, 0.1002. Frictional ratio, meniscus and bottom positions were set as fitted parameters. Time independent noise was also fitted. The detected peaks were integrated and classified as follows: from 0 to 6 S, fragments; from 6 to 9 S, monomer; and from 9 to 20 S, aggregates.

#### **Turbidity Measurement**

[00419] Protein aggregation in the antibody formulation was also characterized by turbidity measurement. Turbidity is a measure of the amount by which the particles in a solution scatter light and, thus, may be used as a general indicator of protein aggregation or denaturation.

[00420] Approximately 3 to 4 ml of formulation sample was transferred into a glass test tube and degassed for 2 minutes using an in-line vacuum system. The degassed sample was then placed into a turbidimeter (2100AN or 2100N, Hatch) sample compartment at room temperature for analysis. The turbidimeter was calibrated with STABLCAL® Stabilized Formazin Turbidity standard (Hatch) at 40, 200, 1000 and 4000 NTU (nephelometric turbidity unit) and verified by analyzing control suspensions of formazin at 3, 6, 18, 30 and 60 NTU.

### **Results**

[00421] SEC was used to monitor antibody aggregate and fragment formation in formulations of A4B4L1FR-S28R stored at three temperature ranges over the course of 9 months. Temperature ranges above the proposed storage temperature, 2-8 °C, were used to stress the formulation and were hoped to simulate the effects of prolonged storage. FIGS. 6 A, B and C present the relative percentage of monomer (purity), aggregates and fragments, respectively, for a single formulation of motavizumab stored at 2-8 °C, 20-24 °C and 38-42 °C. The relative percentage of fragmentation and aggregation increased with both time and temperature. For a single temperature range, however, both the fragmentation and aggregation rate were constant. This finding proved that a higher storage temperature would accurately simulate an accelerated time scale.

[00422] The logarithm of the estimated rates of fragmentation/aggregation also showed a linear dependence to the reciprocal of the storage temperature (FIG. 7). Once this linearity is established, it is then possible to predict the rate of aggregation/fragmentation of a given formulation at any temperature or, more importantly, the formulation characteristics at any time at such temperature.

[00423] FIG. 8 presents a representative SEC profile of the antibody formulation after storage at 38-42 °C with 70-80 % relative humidity for 1 month. Under these conditions, SEC was able to clearly separate antibody aggregates and fragments from monomers. However, at low relative levels of aggregates/fragments, the peaks identified as aggregates and fragment I in FIG. 8 begin to become less distinct and merge into the shoulders of the monomer peak. Such shoulders cannot be accurately analyzed.

[00424] As an alternative, AUC was investigated as a method to characterize low relative levels of aggregation and fragmentation in antibody formulations. FIG. 9 and Table 7 compare the AUC and SEC analysis of formulation samples at initial, 9 month and 14 month time points (the 9 and 14 month samples had been stored at 38-42 °C with 70-80 % relative humidity).

AUC identified two major fragmentation peaks at about 50 KDa and about 90 KDa. AUC was also able to better resolve the fragmentation and aggregation peaks. For the 9 month sample, SEC did not resolve the large fragment peak, while AUC was clearly capable of resolving it. For the 14 month sample, the large fragment peak in SEC was observed as a shoulder of the monomer peak and, when integrated, resulted in a higher fragment I percent than that determined by AUC. Aggregate values for AUC and SEC were comparable. AUC estimates of the molecular mass of the aggregate peak indicated that the majority of the aggregates were antibody dimers.

**[00425]** Compared to SEC, AUC is also able to better resolve differing species of a given macromolecule. It is, however, first necessary to establish the proper sample dilution, as the noise/signal ratio of AUC is dependent on the concentration of antibody in the sample (FIG. 10). For the described formulation of A4B4L1FR-S28R (100 mg/ml in 25 mM histidine-HCl, pH 6.0), a 200 fold dilution was used -- resulting in a sample antibody concentration of 0.5 mg/ml. Under these conditions, AUC was able to resolve the slight changes in formulation composition observed over 5 days of storage at 38-42 °C with 70-80 % relative humidity (FIG. 11).

TABLE 7. COMPARISON OF AUC AND SEC ANALYSIS OF motavizumab FORMULATIONS AT INITIAL, 9-MONTH AND 14-MONTH TIME POINTS

Samples	AUC			SEC		
	Fragments%	Monomer%	Aggregates%	Fragments%	Monomer%	Aggregates%
Initial	0.0	99.2	0.8	0.0	99.5	0.5
9-month	7.5	89.3	3.2	3.3	93.7	3.0
14-month	24.5	64.7	10.8	28.8	60.5	9.8

**[00426]** As a general indicator of protein aggregation, the antibody formulation may also be monitored for changes in turbidity. Four lots of a formulation containing concentrations of antibody at about 100 mg/ml were measured for turbidity using a HACH turbidimeter after storage at 38-42 °C for one month (Table 8). The results indicate that the turbidity levels of the differing lots of the formulation had comparable turbidity measurements, comparable NTU, but that one lot showed an elevated measurement. Elevated turbidity may indicate a higher level of aggregation or an increased number/ increased size of particles.

TABLE 8. TURBIDITY VALUES OF FOUR LOTS OF A motavizumab FORMULATION

MAb	Lot	Concentration (mg/ml)	Turbidity Value (NTU)
A4B4L1FR-S28R	A	100	5.8
	B	100	7.1
	C	100	6.1
	D	100	5.6
	E	100	5.7

## 6.2 EXAMPLE: CHARACTERIZATION OF ANTIBODY FRAGMENTS AND FORMULATION PARTICLE SIZE DISTRIBUTION

[00427] This example illustrates the characterization of antibody fragments as identified by AUC or SEC. Antibody A4B4L1FR-S28R is used in this example. Unless otherwise indicated, all antibody samples in this example were formulated at a concentration of 100 mg/ml in 25 mM histidine-HCl, pH 6.0. Further storage conditions are reported in the section describing experimental results.

### Materials and Methods

#### Liquid Chromatography Mass Spectrometry (LC-MS)

[00428] The SEC fragment peaks were collected and digested with N-Glycosidase F, also known as PNGase F, at 37 °C overnight. PNGase F is an amidase that cleaves between the innermost GlcNAc and asparagine residues of high mannose, hybrid and complex oligosaccharides on N-linked glycoproteins. The deglycosylated sample (approximately 7.5 µL) was mixed with approximately 42.5 µL of reducing buffer (2.5 mg/mL DTT, 6.0 M guanidine HCl, pH 8.2) and kept at 56 °C in a water bath for 60 minutes. Neat 4-vinylpyridine (Aldrich Chem. Co., WI) (approximately 0.5 µL) was then added to the sample, and the reaction mixture was held at ambient temperature for 30 minutes. The deglycosylated, reduced and alkylated

sample was immediately loaded onto a reversed phase column to separate the modified samples from the reactants, and to analyzed by LC-ESI-MS.

[00429] Deglycosylated, reduced, and alkylated samples were fractionated using a reversed phase column (Jupiter 5 $\mu$ m C4, 300 Å, 250 x 2.00 mm, Phenomenex) with a binary gradient HPLC system (Agilent 1100). Mobile phase A consisted of 30% acetonitrile in water with 0.1% trifluoroacetic acid and mobile phase B consisted of 50% acetonitrile in water with 0.1% trifluoroacetic acid. The samples were separated using a linear gradient of 30-50% acetonitrile in water, over 16 min. with a flow rate of 200  $\mu$ L/min. The column effluent was directed to a UV detector and then split 1:1, one half going to a switching valve on the Ion Trap mass spectrometer (LTQ, ThermoElectro, San Jose, CA), and the remaining half to waste. The switching valve diverted the column effluent flow to the mass spectrometer only between the 15 and 30 minutes portion of the chromatographic run.

[00430] A mixture of caffeine, L-methionyl-arginyl-phenylalanyl-alanine acetate·H<sub>2</sub>O, and Ultramark 1621 was used to calibrate the ion-trap mass spectrometer according to the manufacturer's instruction. The ESI-MS data were acquired in positive ESI full scan mode. The BioWork deconvolution program (ThermoFinnigan) was used to reconstruct the mass spectra and obtain the molecular masses of the peptides/proteins from their original mass spectra.

#### **Disulfide Bond Determination**

[00431] Test samples of antibody were denatured in 10 mM phosphate buffer, 250 mM NaCl, 5 mM NEM, 6 M Guanidine, pH 7.0 at 37 °C for 1 to 3 hr. The denatured samples were then diluted 6 fold with 100 mM phosphate buffer, 0.1 mM EDTA, pH 7.0, to which Lys-C was added at a 1:10 enzyme to protein ratio. The reaction mixtures were incubated at 37 °C for 16 to 24 hours. Half of the reaction mixture was reduced by adding 5-10  $\mu$ L of 100 mM DTT and incubated at 37 °C for 1 hr.

[00432] Lys-C digests were separated by reverse-phase HPLC (Phenomenex Jupiter 5m C18 column; 250 x 2.1 mm) and analyzed by an UV-detector and an on-line LCQ or LTQ Ion Trap mass spectrometer (ThermoElectron). The RP-HPLC mobile phase A was 0.1% TFA in H<sub>2</sub>O and the mobile phase B was 0.1% TFA in acetonitrile. The peptides were eluted at a flow rate of 0.2 mL/min with the following gradient:

[00433] 0-2 min, 5% Mobile Phase B

- [00434] 2-32 min, 5-20% Mobile Phase B
- [00435] 32-132 min, 20-40% Mobile Phase B
- [00436] 132-152 min, 40-60% Mobile Phase B
- [00437] 152-155 min, 60-95% Mobile Phase B
- [00438] The column eluant was diverted to waste directly after the UV-detector during the first 15 min to avoid salt contamination of the LCQ source.

### **Particle Counting**

- [00439] The number and size of particles in a solution was characterized by a Beckman Coulter Multisizer 3.

### **Results**

[00440] To characterize aggregates and fragments identified by SEC, fragment fractions were collected from the SEC chromatographic system and analyzed by LC-MS (antibody fragment I and antibody fragment II, FIGS. 12 and 13, respectively). The predominant fragments, above the detection limit of LC-MS, were identified for both fragment peaks (antibody type I fragment and antibody type II fragment) (FIG. 14 and Table 9). Antibody Type I and Antibody Type II fragments were generated by cleavage of the heavy chain in one of the hinge regions of the antibody. Observed cleavage sites were between serine 222 and cysteine 223, cysteine 223 and aspartic acid 224, between aspartic acid 224 and lysine 225, between lysine 225 and threonine 226, between threonine 226 and histidine 227, between histidine 227 and threonine 228, and between threonine 228 and cysteine 229.

[00441] A comparison of peptide maps using reduced and non-reduced conditions of LC-MS/MS was also used to detect disulfide bond scrambling or other covalent modification in the monoclonal antibodies. The profile comparison for aggregates, monomer and fragments indicates that only a low level of disulfide bond scrambling existed in the aggregates (FIGS. 15 and 16). The results also suggest that most of the aggregates were non-covalently linked aggregates, as no significant profile change compared to that of monomer was observed.

Table 9. LC MS IDENTIFICATION OF motavizumab FRAGMENTS AFTER STORAGE OF ANTIBODY FORMULATION AT 38-42°C FOR 1 MONTH

	Sequence	Calculated MW	Measured MW	MW Accuracy
Reference Standard	Light Chain	23654.1	23654.9	0.0000
	Heavy Chain	50617.68	50619.6	0.004%
Fragment II	Light Chain	23654.1	23655.2	0.0000
	H1-222+O	24360.69	24364.6	0.016%
	H1-223+O	24568.97	24571.1	0.009%
	H1-224+O	24684.06	24686	0.008%
	H1-226+O	24913.34	24913.5	0.001%
	H1-227+O	25050.48	25053.2	0.011%
	H1-222	24344.69	24346.2	0.006%
	H1-223	24552.97	24554.9	0.008%
	H1-224	24668.06	24671.5	0.014%
	H1-226	24897.34	24899.9	0.010%
	H1-227	25034.48	25037.9	0.014%
Fragment I	Light Chain	23654.1	23655.2	0.0000
	H228-449+O	25599.2	25604.6	0.021%
	H227-449+O	25736.34	25742	0.022%
	H226-449+O	25837.44	25843.3	0.023%
	H225-449+O	25965.61	25972.7	0.027%
	H224-449+O	26080.7	26085.7	0.019%
	H1-449+O	50633.68	50640.7	0.014%
	H1-449	50617.68	50624.1	0.013%

[00442] A multisizer was also used to characterize the particle size distribution of the antibody formulation. A test sample of formulation at 100 mg/ml was analyzed in a Beckman Coulter Multisizer 3 (Table 10).

TABLE 10. PARTICLE ANALYSIS OF motavizumab SAMPLE AFTER STORAGE OF ANTIBODY FORMULATION AT 38-42°C FOR 1 MONTH

Size	Dilution 1,run 1	Dilution 1,run 2	Dilution 1,run 3	Dilution 2,run 1	Dilution 2,run 2	Dilution 2,run 3	Average
$\mu\text{m}$	Particle/mL	Particle/mL	Particle/mL	Particle/mL	Particle/mL	Particle/mL	Particle/mL
2-4	3.08E+05	3.11E+05	3.09E+05	2.81E+05	2.83E+05	2.82E+05	2.96E+05
4-10	3.93E+04	3.79E+04	3.75E+04	3.61E+04	3.54E+04	3.32E+04	3.66E+04
10-20	3.33E+03	3.47E+03	2.69E+03	6.11E+03	3.71E+03	3.74E+03	3.84E+03
20-30	5.97E+02	3.06E+02	2.55E+02	1.01E+03	3.06E+02	2.40E+02	4.52E+02
30-40	1.02E+02	5.10E+01	0.00E+00	1.48E+02	5.10E+01	5.10E+01	6.72E+01
40-60	5.10E+01	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	8.50E+00
2-60 total	3.51E+05	3.52E+05	3.50E+05	3.25E+05	3.22E+05	3.19E+05	3.37E+05

### 6.3 KINETIC ANALYSIS OF BINDING OF A4B4L1FR-S28R BY BIACORE™

[00443] The kinetics of the interactions of A4B4L1FR-S28R and palivizumab with RSV F-protein were determined by surface plasmon resonance (see, *e.g.*, Jonsson et al., 1991, Biotechniques 11(5):620-627 and Johne, B. (1989). Epitope mapping by surface plasmon

resonance in the BIAcore. Molecular Biotechnology 9(1):65-71) using a BIAcore 3000 instrument (BIAcore, Inc., Piscataway, NJ). A recombinantly produced, C-terminally truncated RSV (A2 strain) F protein (Wathen et al., 1989, J Infect Dis 159(2):255-264) was used as the antigen for these studies. The truncated F protein, lacking the membrane anchor, was produced as a secreted product using a recombinant baculovirus expression system and was purified by successive chromatography steps on concanavalin-A and Q-sepharose columns. Purified F protein was covalently coupled to an N-hydroxysuccinimide-N-ethyl-N'-[3-diethylaminopropyl]-carbodiimide (EDC/NHS) activated CM5 sensor chip at a low protein density according to the manufacturer's protocol; unreacted active ester groups were blocked with 1 M ethanolamine. For reference purposes, a blank surface, containing no antigen, was prepared under identical immobilization conditions.

**[00444]** For kinetic measurements, a serial 2-fold dilution series of each mAb from 100 nm – 0.2 nm, made in instrument buffer (HBS/Tween-20, BIAcore, Inc.), was injected over the F-protein and reference cell surfaces, which are connected in series. In each analysis, following the dissociation phase, the remaining bound antibody was removed from the sensor chip by passing a brief pulse of 100 mM HCl over the surface. Once an entire data set was collected, the resulting binding curves were globally fitted to a 1:1 Langmuir binding model using BIAevaluation software (BIAcore, Inc., Piscataway, NJ). This algorithm calculates both the association rate ( $k_{on}$ ) and the dissociation rate ( $k_{off}$ ), from which the apparent equilibrium binding constant,  $K_D$ , for each antibody was deduced as the ratio of the two rate constants,  $k_{off} / k_{on}$ . A more detailed explanation of how the individual rate constants are derived can be found in the BIAevaluation Software Handbook (BIAcore, Inc., Piscataway, NJ).

**[00445]** Kinetic analysis of binding by BIAcore evaluation (Table 11) revealed that, under the conditions of a low-density surface that were employed, A4B4L1FR-S28R (motavizumab) had an approximately 70-fold greater affinity for RSV F protein than palivizumab. The increased affinity of motavizumab for the RSV F protein is attributed to a 4-fold increase in the association rate and an approximately 17-fold decrease in the dissociation rate. Since the rate at which motavizumab dissociates from the F protein surface approaches the detection limits of the BIAcore 3000 instrument, the dissociation rate generated for motavizumab is an estimation.

**Table 11. Kinetic Analysis of Binding**

mAb	$k_{on}$ ( $M^{-1}s^{-1}$ )	$k_{off}$ ( $s^{-1}$ )	$K_D$ (pM)
palivizumab	1.14 E+05	3.95 E-04	3460
motavizumab	4.73 E+05	2.35 E-05	50



#### 6.4 EXAMPLE: MICRONEUTRALIZATION ASSAY

[00446] Neutralization of the antibodies of the present invention were determined by microneutralization assay. This microneutralization assay is a modification of the procedures described by Anderson et al. (1985, J. Clin. Microbiol. 22:1050-1052, the disclosure of which is hereby incorporated by reference in its entirety). The procedure used here is described in Johnson et al., 1999, J. Infectious Diseases 180:35-40, the disclosure of which is hereby incorporated by reference in its entirety. Antibody dilutions were made in triplicate using a 96-well plate. Ten TCID<sub>50</sub> of respiratory syncytial virus (RSV – Long strain) were incubated with serial dilutions of the antibody (or Fabs) to be tested for 2 hours at 37° C in the wells of a 96-well plate. RSV susceptible HEp-2 cells ( $2.5 \times 10^4$ ) were then added to each well and cultured for 5 days at 37° C in 5% CO<sub>2</sub>. After 5 days, the medium was aspirated and cells were washed and fixed to the plates with 80% methanol and 20% PBS. RSV replication was then determined by F protein expression. Fixed cells were incubated with a biotin-conjugated anti-F protein monoclonal antibody (pan F protein, C-site-specific mAb 133-1H) washed and horseradish peroxidase conjugated avidin was added to the wells. The wells were washed again and turnover of substrate TMB (3,3',5,5'-tetramethylbenzidine) was measured at 450 nm. The neutralizing titer was expressed as the antibody concentration that caused at least 50% reduction in absorbency at 450 nm (the OD<sub>450</sub>) from virus-only control cells. The results from the assay for the monoclonal antibodies and Fab fragments listed in Table 2 are shown in Table 11, *supra*, and Table 12, *infra*.

**Table 12. End Point RSV Microneutralization Titer Of High On Rate Mutant IgG and Fab**

Molecule	Mean IC50 (Curve) μg/ml	STDEV Curve IC50	Fold Difference (Curve IC50)	Mean IC50 (Control) μg/ml	STDEV Control IC50	Fold Difference (Control IC50)	n (assay repeat)
**palivizumab	0.4527	0.208	-	0.5351	0.238	-	8
**A1e9	0.0625	0.0268	7	0.0645	0.223	8	3
**A17d4(1)	0.0342	0.022	13	0.0354	0.0187	15	4
**P11d4	0.0217	0.0331	21	0.0289	0.0110	19	5
**P12f2	0.0231	0.0141	20	0.0223	0.0083	24	6
**A8c7	0.0337	0.0309	13	0.0383	0.0283	14	5
**A12a6	0.0357	0.0316	13	0.0354	0.0261	15	7
**P12f4	0.0242	0.0163	19	0.0235	0.0076	23	7
**A13c4	0.0376	0.0268	12	0.0375	0.0213	14	6
**A4B4	0.0171	0.0018	27	0.0154	0.00417	35	2
*A1e9	0.157	-	3	0.125	-	4	1
*A17d4(1)	0.0179	-	25	0.0171	-	31	1
*P11d4	>1.00	-	-	>1.00	-	-	1
*P12f2	0.0407	0.0112	11	0.0326	0.00905	16	2
*A8c7	0.177	-	3	0.157	-	34	1
*A12a6	0.0287	0.00417	16	0.0310	0.00982	17	2
*P12f4	0.0464	0.00791	10	0.0351	0.0126	15	2

*A13c4	0.0264	0.00141	17	0.0258	0.00071	21	2
*A4B4	0.0414	-	11	0.0411	-	13	1
*A13a11	0.120	0.0222	4	0.1022	0.0260	5	2
*A1h5	0.194	0.462	2	0.176	0.0625	3	2

\*\* Monoclonal Antibody

\* Fab Fragment

## 6.5 RSV MICRONEUTRALIZATION ASSAY

[00447] The ability of A4B4L1FR-S28R (motavizumab) and palivizumab to inhibit the *in vitro* replication of RSV (Long strain) was evaluated using a RSV microneutralization assay. This assay is a modification of the procedure of Anderson et al. (Anderson et al., 1985, J Clin Microbiol 22: 1050-1052) as described by Johnson et al. (Johnson et al., 1997, J Infect Dis 176: 1215-1224). Antibody dilutions were made in duplicate to quadruplicate wells of a 96-well plate. Approximately 100-1000 TCID<sub>50</sub> of RSV (Long) were added to each dilution well and incubated for two hours at 37°C. Low passage, RSV susceptible HEp-2 cells (2.5x10<sup>4</sup>) were then added to each well and cultured for five days at 37° C in a humidified 5%CO<sub>2</sub> incubator. After four or five days the cells were washed with PBS - 0.1% Tween 20 and fixed to the plate with 80% acetone with 20% PBS. RSV replication was determined by quantitation of F protein expression using an F protein-specific ELISA. Fixed cells were incubated with the C-site specific, pa RSV F protein mAb 133-1H (Chemicon, Inc.), washed, and then incubated with horseradish peroxidase-conjugated goat anti-mouse IgG and washed again. The peroxidase substrate TMB (3,3',5,5'-tetramethylbenzidine) was added to each well and the reaction was stopped after twenty minutes by the addition of 2 M H<sub>2</sub>SO<sub>4</sub>. Substrate turnover was measured at 450 nm (OD450) using a microplate reader. The neutralizing titer is expressed as the antibody concentration resulting in at least a 50% reduction in the OD450 value from control wells with virus only (IC<sub>50</sub>). The results of this assay, shown in FIG. 17, indicate that motavizumab (average IC<sub>50</sub> = 18 ng/ml) is approximately 18-fold more potent than palivizumab (average IC<sub>50</sub> = 315 ng/ml).

## 6.6 RSV MICRONEUTRALIZATION ASSAY WITH CYNOMOLGUS BAL SAMPLES

[00448] The ability of motavizumab present in the lungs of treated animals to inhibit the *in vitro* replication of RSV was evaluated using the RSV microneutralization assay. Four juvenile female cynomolgus monkeys (average weight 2.0 kg) were sedated with Telazol and dosed intravenously (i.v.) with motavizumab at 30 mg/kg body weight via the saphenous vein using an external infusion pump. Four days later, the animals were anesthetized with Telazol

and a bronchial alveolar lavage (BAL) was performed on one lobe of the right lung with phosphate buffered saline (PBS). Titers of motavizumab in the BAL fluid were determined using a motavizumab-specific ELISA. The BAL samples were tested undiluted and at serial 2-fold dilutions in the RSV microneutralization assay as above with purified motavizumab included as a control. The results of this assay, shown in FIG. 18, show that motavizumab retains full RSV neutralizing activity in the lungs of cynomolgus monkeys four days after infusion.

### **6.7 RSV FUSION INHIBITION ASSAY**

[00449] The ability of the antibodies of the invention to block RSV-induced fusion after viral attachment to the cells is determined in a fusion inhibition assay. This assay is identical to the microneutralization assay, except that the cells are infected with RSV (Long) for four hours prior to addition of antibody (Taylor et al., 1992, J. Gen. Virol. 73:2217-2223).

### **6.8 PHYSICAL CHARACTERIZATION**

[00448] The example illustrates the physical characteristics of motavizumab and palivizumab. A number of parameters were examined including the T<sub>m</sub> and pI. In addition, the aggregation rates and viscosity profiles of motavizumab and palivizumab were determined.

## **Materials and Methods**

### **Generation of Antibody Fragments**

[00449] Fab and Fc domains were generated from full length palivizumab antibody using papain. A commercial kit from Pierce (ImmunoPure Fab Preparation Kit Pierce Product # 44885: ImmunoPure IgG Binding Buffer, ImmunoPure IgG Elution Buffer, AffinityPak Immobilized Protein A Column, Immobilized Papain, Cysteine monohydrochloride, Phosphate Buffer, and Serum Separators) was used to digest the intact antibodies. The enzymology was optimized to achieve the best cleavage of the Mab in a reasonable time. Fab and Fc domains were generated from palivizumab using the following steps: a) adding antibody to papain and incubating overnight at 37°C, ~ 10 mg of IgG per digestion; b) separating crude digest from immobilized enzyme; c) applying digest to Protein A column; d) eluting the Fab fragment in unretained fraction at pH-8.0; e) eluting the Fc fragment at pH-3.0; and f) dialyzing the fragments into a required buffer.

**Differential Scanning Calorimetry**

[00450] Thermal melting temperatures ( $T_m$ ) were measured with a VP-DSC (MicroCal, LLC) using a scan rate of 1.0°C/min and a temperature range of 25 – 120°C. A filter period of 8 seconds was used along with a 5 minute pre-scan thermostating. Samples were prepared by dialysis into 10 mM Histidine-HCl, pH 6 using Pierce dialysis cups (3.5 kD). Average Mab concentrations were 50 µg/mL as determined by  $A_{280}$ . Melting temperatures were determined following manufacturer procedures using Origin software supplied with the system. Briefly, multiple baselines were run with buffer in both the sample and reference cell to establish thermal equilibrium. After the baseline was subtracted from the sample thermogram, the data were concentration normalized and fitted using the deconvolution function.

**Isoelectric Focusing Gel Electrophoresis**

[00451] Isoelectric points were determined using a Pharmacia Biotech Multiphor 2 electrophoresis system with a multi temp 3 refrigerated bath recirculation unit and an EPS 3501 XL power supply. Pre-cast ampholine gels (Amersham Biosciences, pI range 2.5-10) were loaded with 5 µg of protein. Broad range pI marker standards (Amersham, pI range 3-10, 8 µL) were used to determine relative pI for the Mabs. Electrophoresis was performed at 1500 V, 50 mA for 105 minutes. The gel was fixed using a Sigma fixing solution (5x) diluted with purified water to 1x. Staining was performed overnight at room temperature using Simply Blue stain (Invitrogen). Destaining was carried out with a solution that consisted of 25% ethanol, 8% acetic acid and 67% purified water. Isoelectric points were determined using a Bio-Rad Densitometer relative to calibration curves of the standards.

**Viscosity Profile**

[00452] Viscosities of mAB solutions were measured using a ViscoLab 4000 Viscometer System (Cambridge Applied Systems) equipped with a ViscoLab Piston (SN:7497, 0.3055", 1-20 cP) and S6S Reference Standard (Koehler Instrument Company, Inc.). The viscometer was connected to a water bath and equilibrate the system to 20°C. Piston was checked using S6S viscosity reference standard (8.530 cP @ 20.00°C). Piston was also checked using RODI H<sub>2</sub>O (1.00 cP @ 20.0°C). The piston was cleaned and rinsed thoroughly with soap and water between measurements of each different solution type. Each Mab was in 10 mM Histidine-HCl, pH 6 at a concentration of 100 mg/mL. The system was then cooled to  $\leq 2^\circ\text{C}$ . When the system temperature was at or below 2°C, sample was loaded into the chamber and the piston was lowered into the sample. After sample was equilibrated to the temperature of the chamber, measurement was initiated. The temperature was increased at 1°C increments every 7-10

minutes to a final temperature of  $\geq 25^{\circ}\text{C}$ . The temperature was adjusted on the water bath but the recorded temperature was what was displayed on the viscometer. The viscosity result was recorded immediately prior to increasing the temperature. The piston remained in motion during measurements to minimize the need for re-equilibration.

### **Aggregation Rate**

[00453] Aggregation profiles over a range of temperatures were determined by HPSEC. Specifically, approximately 250  $\mu\text{g}$  of, for example, the antibody or antibody fragment that immunospecifically binds to a target antigen (approximately 25  $\mu\text{l}$  of a liquid formulation comprising 10 mg/ml said antibody or antibody fragment) was injected onto a TosoH Biosep TSK G3000SWXL column (7.8 mm x 30 cm) fitted with a TSK SW x1 guard column (6.0 mm CX 4.0 cm). The antibody or antibody fragment was eluted isocratically with 0.1 M disodium phosphate containing 0.1 M sodium sulfate and 0.05% sodium azide, at a flow rate of 0.8 to 1.0 ml/min. Eluted protein was detected using UV absorbance at 280 nm. A suitable reference standard was run in the assay as a control, and the results were reported as the area percent of the product monomer peak compared to all other peaks excluding the included volume peak observed at approximately 12 to 14 minutes. Peaks eluting earlier than the monomer peak were recorded as percent aggregate.

### **Results**

[00454] Differential Scanning Calorimetry (DSC) was used to examine the melting curve of the full length palivizumab (FIG. 19, top). Fab and Fc domain fragments were generated from palivizumab and the purified fragments were analyzed individually by DSC (FIG. 19, bottom). The results show that individual  $T_m$  peaks in a full antibody may be assigned to individual domains. In particular, the largest peak represents the  $T_m$  of the Fab portion of a full length antibody. The  $T_m$  of the palivizumab Fab is about  $87.6^{\circ}\text{C}$ .

[00455] A similar analysis was performed on motavizumab (data not shown). The  $T_m$  of the motavizumab Fab was found to be significantly higher, about  $93.1^{\circ}\text{C}$ . This finding is unexpected as these two molecules differ by only 13 amino acids.

[00456] To further characterize these molecules, the pI for each full length mAb was determined by isoelectric focusing gel electrophoresis. motavizumab has a pI of 9.0 and palivizumab was found to have a pI of 9.1. The Fab- $T_m$  and mAb-pI values for each antibody are plotted in FIG. 20 for comparison.

[00457] The viscosities of 100 mg/ml solutions of motavizumab and palivizumab were respectively examined over a range of temperatures from about  $2^{\circ}\text{C}$  to about  $25^{\circ}\text{C}$ . The viscosity of motavizumab ranged from a high of about 6.0 cP at  $2^{\circ}\text{C}$  to a low of about 3.0 cP at about  $25^{\circ}\text{C}$ .

°C. The viscosity of palivizumab ranged from a high of about 4.5 cP at 2 °C to a low of about 2.0 cP at about 25 °C (FIG. 21).

[00458] The aggregation rates of palivizumab and motavizumab were plotted against the Fab T<sub>m</sub> for each antibody (FIG. 22). A correlation between Fab T<sub>m</sub> and reduced aggregation rates is seen. motavizumab, which has a significantly higher Fab T<sub>m</sub>, is much less prone to forming aggregates than palivizumab.

## 7. EQUIVALENTS

[00459] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[00460] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

WHAT IS CLAIMED IS:

1. An antibody formulation comprising a full length IgG<sub>1</sub> antibody, which antibody immunospecifically binds to an RSV antigen and is not palivizumab, wherein (i) within a predetermined period of time after production no more than a predetermined percentage of the total protein fraction of said formulation is antibody type I and antibody type II fragments, wherein said predetermined period of time is at least about 1 week, and wherein said predetermined percentage is about 0.5%; or (ii) within a month after production and under a temperature of 38-42° C. and a pH of 6.0, less than 5 % of the total protein fraction of said formulation comprises antibody aggregates as determined by size exclusion chromatography (SEC) with UV detection.

2. The formulation of claim 1, wherein within a predetermined period of time after production no more than a predetermined percentage of the total protein fraction of said formulation is antibody type I and antibody type II fragments, wherein said predetermined period of time is at least about 1 week and wherein said predetermined percentage is about 0.5%.

3. The formulation of claim 1 or 2, wherein said RSV antigen is an F protein epitope.

4. The formulation of claim 1 or 2, wherein said RSV antigen comprises the F protein epitope NSELLSLINDMPITNDQKKLMSNN (SEQ ID NO:337).

5. The formulation of claim 1 or 2, wherein said RSV antigen consists of the F protein epitope NSELLSLINDMPITNDQKKLMSNN (SEQ ID NO:337).

6. The formulation of any one of claims 1 to 5, wherein the antibody competitively inhibits the binding of antibody A4B4L1FR-S28R to said RSV antigen.

7. The formulation of any one of claims 1 to 6, wherein the antibody comprises at least one variable heavy (VH) CDR of the antibody A4B4L1FR-S28R, at least two variable heavy (VH) CDRs of the antibody A4B4L1FR-S28R or at least three variable heavy (VH) CDRs of the antibody A4B4L1FR-S28R.

8. The formulation of any one of claims 1 to 6, wherein the antibody comprises at least one variable light (VL) CDR of the antibody A4B4L1FR-S28R, at least two variable light (VL) CDRs of the antibody A4B4L1FR-S28R or at least three variable light (VL) CDR of the antibody A4B4L1FR-S28R.

9. The formulation of any one of claims 1 to 7, wherein the antibody comprises a VH domain of the antibody A4B4L1FR-S28R (SEQ ID NO.:48).

10. The formulation of any one of claims 1 to 6 and 8, wherein the antibody comprises a VL domain of the antibody A4B4L1FR-S28R (SEQ ID NO.:11).

11. An antibody formulation comprising at least 100 mg/ml of a full length IgG<sub>1</sub> antibody comprising a heavy chain having the variable heavy (VH) domain of A4B4L1FR-S28R (SEQ ID NO:48) and a light chain having the variable light (VL) domain of A4B4L1FR-S28R (SEQ ID NO:11), wherein, within 1 month after production and under 38-42° C and pH 6.0, no more than 0.5 % of the total protein fraction of said formulation is antibody type I fragment.

12. An antibody formulation comprising at least 100 mg/ml of a full length IgG<sub>1</sub> antibody comprising a heavy chain having the variable heavy (VH) domain of A4B4L1FR-S28R (SEQ ID NO:48) and a light chain having the variable light (VL) domain of A4B4L1FR-S28R (SEQ ID NO:11), wherein, within 1 month after production and under 38-42° C and pH 6.0, no more than 0.5 % of the total protein fraction of said formulation is antibody type II fragment.

13. The antibody formulation of any one of claims 1 to 12, wherein each said antibody type I fragment comprises a heavy chain C-terminal portion, said heavy chain C-terminal portion has a molecular weight of about 25.6 kD, about 25.7 kD, about 25.8 kD, about 26.0 kD, or about 26.1 kD as determined by Liquid Chromatography Mass Spectrometry (LC-MS) analysis of samples of said stored antibody that have been deglycosylated, reduced and alkylated.

14. The antibody formulation of any one of claims 1 to 12, wherein each said antibody type II fragment comprises a heavy chain N-terminal portion, said heavy chain N-



terminal portion has a molecular weight of about 24.4 kD, about 24.6 kD, about 24.7 kD, about 24.9 kD, or about 25.1 kD as determined by LC-MS analysis of samples of said stored antibody that have been deglycosylated, reduced and alkylated.

15. The formulation of any one of claims 1 to 14, wherein within a month after production and under a temperature of 38-42° C. and a pH of 6.0, less than 5 % of the total protein fraction of said formulation comprises antibody aggregates as determined by size exclusion chromatography (SEC) with UV detection.

16. The formulation of any one of claims 1 to 15, wherein within a month after production and under a temperature of 38-42° C. and a pH of 6.0, the turbidity value of a degassed sample of said formulation is less than about 6.5 NTU.

17. The formulation of any one of claims 1 to 16, wherein within a month after production and under a temperature of 38-42° C. and a pH of 6.0, said formulation comprises a particle profile of less than about  $3.4 \times 10^5$  particles/ml of diameter 2-4  $\mu\text{m}$ , less than about  $4.0 \times 10^4$  particles/ml of diameter 4-10  $\mu\text{m}$ , less than about  $4.2 \times 10^3$  particles/ml of diameter 10-20  $\mu\text{m}$ , less than about  $5.0 \times 10^2$  particles/ml of diameter 20-30  $\mu\text{m}$ , less than about  $7.5 \times 10^1$  particles/ml of diameter 30-40  $\mu\text{m}$ , and less than about 9.4 particles/ml of diameter 40-60  $\mu\text{m}$  as determined by a multisizer.

18. The formulation of any one of claims 1 to 17, within a month after production and under a temperature of 38-42° C. and a pH of 6.0, said antibody type I fragments comprise one or more C-terminal portions of said heavy chain, which heavy chain C-terminal portion comprises amino acid residues 223-449 of said antibody; amino acid residues 224-449 of said antibody, amino acid residues 225-449 of said antibody, amino acid residues 226-449 of said antibody, amino acid residues 227-449 of said antibody, amino acid residues 228-449 of said antibody and amino acid residues 229-449 of said antibody.

19. The formulation of any one of claims 1 to 18, wherein each said antibody type II fragment comprises a heavy chain N-terminal portion, which heavy chain N-terminal portion comprises amino acid residues 1-222 of said antibody, amino acid residues 1-223 of said antibody, amino acid residues 1-224 of said antibody, amino acid residues 1-225 of said

antibody, amino acid residues 1-226 of said antibody, amino acid residues 1-227 of said antibody or amino acid residues 1-228 of said antibody.

20. The formulation of any one of claims 1 to 19, wherein said formulation further comprises histidine.

21. The formulation of claim 20, wherein histidine is at a concentration of about 1 mM to about 100 mM or of about 10 mM to about 50 mM.

22. The formulation of claim 20, wherein the histidine is at a concentration of about 20 mM to about 30 mM, and wherein said formulation further comprises glycine at a concentration of less than 2 mM and is substantially free of surfactants, inorganic salts or other excipients.

23. The formulation of claim 22, wherein histidine is at a concentration of about 25 mM and glycine is at a concentration of about 1.6mM.

24. The formulation of claim 20, wherein said formulation is substantially free of surfactants and inorganic salts.

25. The formulation of claim 20, wherein said formulation is substantially free of other excipients.

26. The formulation of any one of claims 1 to 19, wherein said formulation further comprises an excipient other than a surfactant.

27. The formulation of claim 26, wherein the excipient is glycine.

28. The formulation of claim 27, wherein glycine is at a concentration of less than 150 mM, less than 100 mM, less than 50 mM, less than 3 mM or less than 2 mM.

29. The formulation of claim 36, wherein the formulation has a pH of about 6.0.

30. The formulation of claim 26, wherein the excipient is a saccharide.

31. The formulation of claim 30, wherein the saccharide is sucrose.
32. The formulation of claim 31, wherein the sucrose is at a concentration of about 1% to about 20%.
33. The formulation of claim 26, wherein the excipient is a polyol other than mannitol.
34. The formulation of claim 33, wherein the polyol is polysorbate.
35. The formulation of claim 33, wherein the polyol is Tween, which is at a concentration of about 0.001% to about 1%.
36. The formulation of any one of claims 1 to 35, wherein said formulation has a pH of between about 5.5 to about 7.0.
37. The formulation of claim 36, wherein said formulation has a pH of between about 5.5 to about 6.5.
38. The formulation of any one of claims 1 to 40, wherein the antibody is at a concentration of at least 5 mg/ml, at least 10 mg/ml, at least 20 mg/ml, at least 50 mg/ml, at least 100 mg/ml, at least 110 mg/ml, at least 150 mg/ml or at least 160 mg/ml.
39. The formulation of any one of claims 1 to 38, wherein said antibody formulation comprises an antibody manufactured and purified by a process comprising (a) transformation of a murine myeloma cell line with a recombinant vector capable of directing transcription of mRNA encoding said antibody; (b) maintenance of transformed cells; (c) collection of conditioned media from cultures of transformed cells; (c) cation/anion exchange chromatography; (e) nanofiltration; and (f) hydroxyapatite chromatography.
40. The formulation of claim 1, wherein the antibody comprises at least one CDR of the antibody A4B4L1FR-S28R, at least two CDRs of the antibody A4B4L1FR-S28R, at least three CDRs of the antibody A4B4L1FR-S28R, at least four CDRs of the antibody A4B4L1FR-S28R, at least five CDRs of the antibody A4B4L1FR-S28R or at least six CDRs of the antibody A4B4L1FR-S28R.

41. The formulation of any one of claims 1 to 40, wherein the formulation is in an aqueous carrier,
42. The formulation of claim 41, wherein the aqueous carrier is distilled water.
43. The formulation of any one of claims 1 to 42, wherein the formulation is sterile.
44. The formulation of any one of claims 1 to 43, wherein the formulation is homogenous.
45. The formulation of any one of claims 1 to 44, wherein the formulation has been prepared by a method that does not have a drying step.
46. The formulation of any one of claims 1 to 45, wherein the formulation has been prepared by a method that does not have a lyophilization step.
47. A pharmaceutical dosage form comprising the formulation of any one of claims 1 to 46, which dosage form is suitable for parenteral administration to a human and is in a suitable container.
48. The pharmaceutical unit dosage form of claim 47, wherein the formulation is suitable for subcutaneous, intravenous or intramuscular administration.
49. The pharmaceutical unit dosage form of any one of claims 1 to 46, which dosage form is suitable for aerosol administration to a human and is in a suitable container.
50. A sealed container comprising the formulation of any one of claims 1 to 46.
51. A method of preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a subject, said method comprising administering a prophylactically or therapeutically effective amount of the formulation of any one of claims 1 to 46.
52. The method of claim 51, wherein the formulation is administered parenterally, intramuscularly, intravenously, subcutaneously or intranasally.

53. A method of optimizing an antibody formulation for antibody fragmentation, said method comprising comparing by analytical ultracentrifugation (AUC) the fragmentation levels of a first antibody formulation produced according to a first protocol and a second antibody formulation produced according to a second protocol, which first and second antibody formulations comprise at least 100 mg/ml of a full length IgG<sub>1</sub> antibody comprising a heavy chain having the variable heavy (VH) domain of A4B4L1FR-S28R (SEQ ID NO:48) and the light chain comprising the variable light (VL) domain of A4B4L1FR-S28R (SEQ ID NO:11), wherein the first and second antibody formulations have been stored at 38-42° C, pH 6.0 for 1 month, wherein an antibody formulation is optimized for fragmentation levels if the fragmentation levels in the second antibody formulation are reduced relative to fragmentation levels in the first antibody formulation.

54. A method of optimizing an antibody formulation for antibody fragmentation, said method comprising comparing a first antibody formulation produced according to a first protocol and a second antibody formulation produced according to a second protocol, which first and second antibody formulations comprise at least 100 mg/ml of a full length IgG<sub>1</sub> antibody comprising a heavy chain having the variable heavy (VH) domain of A4B4L1FR-S28R (SEQ ID NO:48) and the light chain comprising the variable light (VL) domain of A4B4L1FR-S28R (SEQ ID NO:11), for the abundance of antibody type I and antibody type II fragments as determined by Liquid Chromatography Mass Spectrometry (LC-MS) analysis of samples of said stored antibody that have been deglycosylated, reduced and alkylated, wherein said first and second antibody formulations have been stored at 38-42° C, pH 6.0 for 1 month, wherein an antibody formulation is optimized for antibody fragmentation if the levels of antibody type I and antibody type II fragments in the second formulation are reduced relative to the levels of antibody type I and antibody type II fragments in the first antibody formulation.

55. The method of claim 54, wherein said antibody type I fragments comprise one or more heavy chain C-terminal portions, which heavy chain C-terminal portion has a molecular weight of about 25.6 kD, about 25.7 kD, about 25.8 kD, about 26.0 kD, or about 26.1 kD and said antibody type II fragments comprise one or more N-terminal portions of said heavy chain, which heavy chain N-terminal portion has a molecular weight of about 24.4 kD, about 24.6 kD, about 24.7 kD, about 24.9 kD, or about 25.1 kD, wherein the molecular weight of said portion is determined by Liquid Chromatography Mass Spectrometry (LC-MS) analysis

of samples of said antibody formulation that have been deglycosylated, reduced and alkylated.

56. The method of any one of claim 53 to 55, wherein said second protocol comprises an additional chromatography purification step.

57. The method of claim 56, wherein said chromatography purification step utilizes a hydroxyapatite column.

58. The method of any one of claim 53 to 55, wherein said first protocol comprises an additional chromatography purification step.

59. The method of claim 58, wherein said chromatography purification step utilizes an rProtein A affinity column.

60. The method of any of claims 53 to 55, wherein said second antibody formulation comprises an antibody manufactured and purified by a process comprising (a) transformation of a murine myeloma cell line with a recombinant vector capable of directing transcription of mRNA encoding said antibody; (b) maintenance of transformed cells; (c) collection of conditioned media from cultures of transformed cells; (c) cation/anion exchange chromatography; (e) nanofiltration; and (f) hydroxyapatite chromatography.

61. The method of any of claims 53 to 55, wherein said second protocol comprises the alteration of a temperature in one or more steps of said first protocol.

62. An antibody comprising a Fab fragment, which immunospecifically binds to an RSV antigen, wherein the  $T_m$  of the Fab fragment is at least about 87 °C, and wherein said antibody is not any of palivizumab, AFFF, P12f2, P12f4, P11d4, Ale9, A12a6, A13c4, A17d4, A4B4, A8c7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L2-15B10, A13a11, A1h5, A4B4(1), A4B4L1FR-S28R (motavizumab), A4B4-F52S, A17d4(1), A3e2, A14a4, A16b4, A17b5, A17f5, and A17h4.

63. The antibody of claim 62, wherein said Fab is different from the Fab of palivizumab.

64. The antibody of claim 62, wherein the antibody comprises a VH domain that is different from the VH domain of palivizumab.

65. The antibody of claim 62, wherein the antibody comprises a VL domain that is different from the VL domain of palivizumab.

66. The antibody of claim 62, wherein the T<sub>m</sub> of the Fab fragment is at least about 90 °C or at least about 93 °C.

67. The antibody of claim 62, wherein the pI of the antibody is between about 8.5 to 9.5 or between about 9.0 to 9.5.

68. The antibody of claim 62, wherein said RSV antigen is an F protein epitope.

69. The antibody of claim 62, wherein said RSV antigen comprises the F protein epitope NSELLSLINDMPITNDQKKLMSNN (SEQ ID NO:337).

70. The antibody of claim 62, wherein the antibody competitively inhibits the binding of antibody A4B4L1FR-S28R to said RSV antigen.

71. The antibody of claim 62, wherein the antibody comprises a VH domain of the antibody A4B4L1FR-S28R (SEQ ID NO:48).

72. The antibody of claim 62, wherein the antibody comprises a VL domain of the antibody A4B4L1FR-S28R (SEQ ID NO:11).

73. The antibody of claim 62, wherein said Fab is the Fab of antibody A4B4L1FR-S28R.

74. An antibody formulation comprising a full length IgG<sub>1</sub> antibody, which immunospecifically binds to an RSV antigen, said formulation having a viscosity of less than about 10.00 cP at any temperature in the range of 1 to 26 °C.

75. An antibody formulation comprising a full length IgG<sub>1</sub> antibody, which immunospecifically binds to an RSV antigen, said formulation having an aggregation rate of less than 15% per day at any temperature in the range of 38 to 42 °C.

76. An an antibody formulation comprising an antibody as claimed in any one of claims 62 to 73, wherein said formulation having a viscosity of less than 10.00 cP at any temperature in the range of 1 to 26 °C.

77. An an antibody formulation comprising an antibody as claimed in any one of claims 62 to 73, wherein said formulation having an aggregation rate of less than 15% per day at any temperature in the range of 38 to 42 °C.

78. A method of preventing, treating, or ameliorating one or more symptoms associated with a RSV infection in a subject, said method comprising administering a prophylactically or therapeutically effective amount of an antibody formulation comprising the antibody of any one of claims 62 to 73 or the antibody formulation of claims 74 to 77.

79. The method of claim 51 or 78, wherein RSV infection is an upper respiratory tract infection.

80. The method of claim 78, wherein the formulation is administered parenterally, intramuscularly, intravenously, subcutaneously or intranasally.

81. The method of claim 51 or 78, wherein said one or more symptoms are one or more of otitis media, asthma, and wheezing.



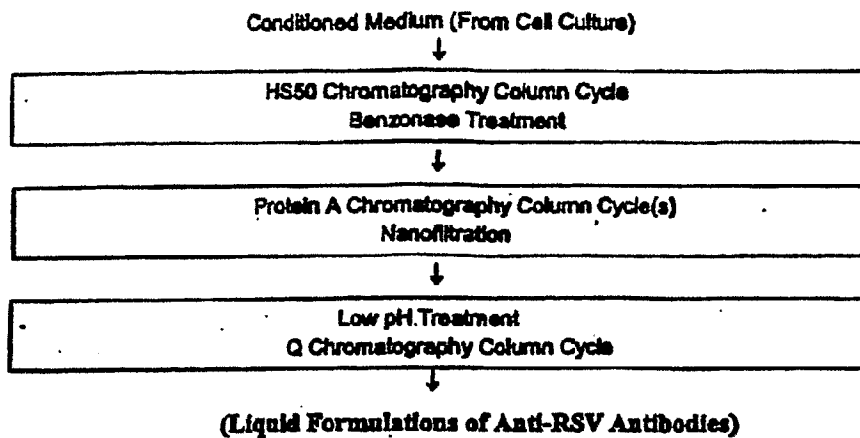
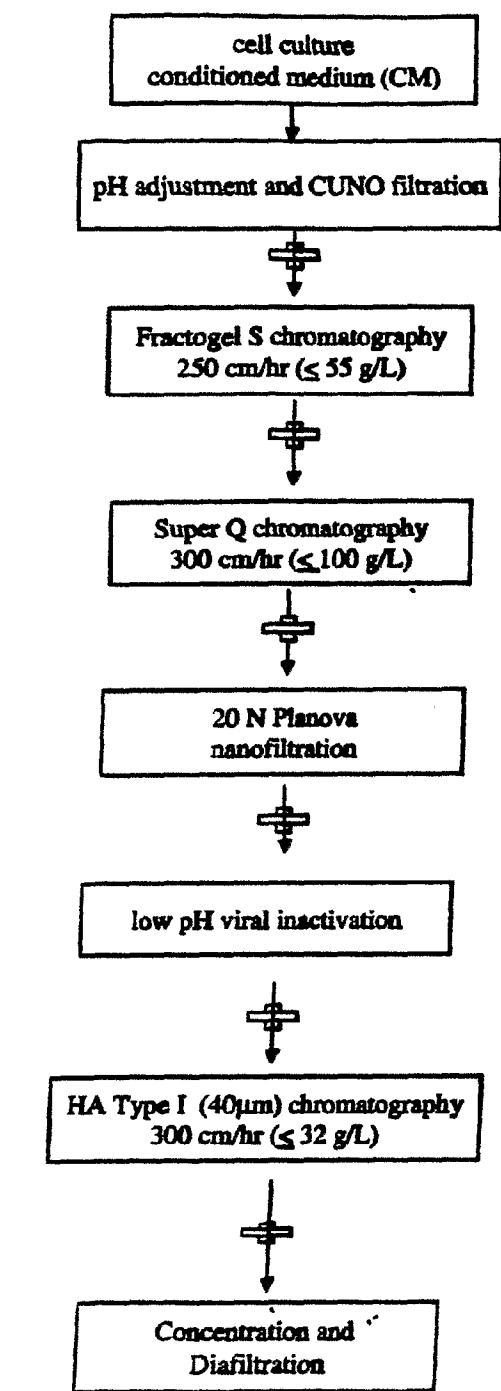


FIG. 1



 filtration required

FIG. 2

A

DIQMTQSPST LSASVGDRVT ITCKCOLSVGYMH WYQOKPG 40  
CDR L1

KAPKLLY DTSKLAS GVP8R FGSGSGTEF TLTISSLOPD 80  
CDR L2

DFATYYC FGSGYPFT FGGTKLEK 108  
CDR L3

B

QVTLRESGPA LVKPTQTLTL TCTFSGFSL TSGMSVG WIR 40  
CDR H1

OPPGKALEWL A DIWDDKKDYNPSLKS RLT ISKDTSKNOV 80  
CDR H2

VLKVTNMDPA DIATYYCAR SMITNWFYDV W GAGTTVTVSS 120  
CDR H3

Fig. 3

A

DIQMTOSPST LEASVGDRVT ITCSASSVGYMH WYQOKPG 40  
CDR L1

KAPKLLY DTSLAS GVPGR NSGSGSTEF TLTSSLOPD 80  
CDR L2

DFATYYC FGSGYPFT FGGG TKVEK 108  
CDR L3

B

QVTLRESGPA LVKFTQTLTL TCTSGFSL TSGMSVG WIR 40  
CDR H1

OPPGKALEWL A DIWVDDKKDYNPSLKS RLT ISKDTSKNOV 80  
CDR H2

VLKVTNMDPA DTATYYCAR SMTNWYFDV WSGGTTVTVSS 120  
CDR H3

FIG. 4

Nucleotide and Translated Amino Acid Sequence of the MEDI-524  
VH

1		15	
	CAG GTC ACA CTG AGG GAG TCT GGT CCT GCG CTG GTG AAA CCC ACA		
	Q V T L R E S G P A L V K P T		MEDI-524 Synagis®
16		30	
	CAG ACC CTC ACA CTG ACC TGC ACC TTC TCT GGG TTT TCA CTG AGC		
	Q T L T L T C T P S G P S L S		MEDI-524 Synagis®
31		45	
	ACT GGC GGT ATG AGT GTA GGC TGG ATT CGT CAG CCC CCA GGG AAG		
	<u>T A G M S V G</u> W I R Q P P G K		MEDI-524 Synagis®
46		60	
	GCC CTG GAG TGG CTT GCA GAC ATT TGG TGG GAT GAC AAA AAG CAC		
	A L E W L A <u>D I W W D D K K</u> H		MEDI-524 Synagis®
61		75	
	TAT AAT CCA TCC CTG AAG GAC CGG CTC ACA ATC TCC AAG GAT ACC		
	<u>Y N P S L K D</u> R L T I S K D T		MEDI-524 Synagis®
76		90	
	TCC AAA AAC CAG GTG GTC CTT AAA GTG ACC AAC ATG GAC CCT GCT		
	S K N Q V V L K V T N M D P A		MEDI-524 Synagis®
91		105	
	GAT ACT GCC ACT TAC TAC TGT GCT CGG GAT ATG ATC TTC AAC TTC		
	D T A T Y Y C A R <u>D M I F N F</u>		MEDI-524 Synagis®
106		120	
	TAC TTC GAT GTC TGG GGC CAG GGG ACC ACG GTC ACC GTG AGC TCA		
	<u>Y F D V</u> W G Q G T T V T V S S		MEDI-524 Synagis®
	A		

Fig. 5A

# Nucleotide and Translated Amino Acid Sequence of the MEDI-524 VL

1	GAT ATC CAG ATG ACC CAG TCT CCT TCC ACC CTG TCT GCA TCT GTA	15	
	D I Q M T Q S P S T L S A S V		MEDI-524 Synagis®
16	GGA GAC AGA GTC ACC ATC ACT TGC AGC GCC AOC TCG CGC GTA GGT	30	
	G D R V T I T C <u>E A S E E V G</u> K C Q L S		MEDI-524 Synagis®
31	TAC ATG CAC TGG TAC CAG CAG AAA CCC GGG AAA GCC OCT AAG CTC	45	
	<u>Y M H</u> W Y Q Q K P G K A P K L		MEDI-524 Synagis®
46	CTG ATC TAT GAC ACT AGT AAA CTG GCT TCT GGG GTC CCA TCA AGG	60	
	L I Y <u>D T S K L A S</u> G V P S R		MEDI-524 Synagis®
61	TTC AGC GGC AGT GGA TCT GGG ACA GAA TTC ACT CTC ACC ATC AGC	75	
	F S G S G S G T E F T L T I S		MEDI-524 Synagis®
76	AGC CTG CAG OCT GAC GAT TTT GCA ACT TAT TAC TGC TTT CAG GGG	90	
	S L Q P D D F A T Y Y C <u>P Q G</u>		MEDI-524 Synagis®
91	AGT GGG TAC CCA TTC ACG TTC GGA GGG GGG ACC AAG GTC GAA ATA	105	
	<u>S G Y P P T</u> F G G G T K V E I		MEDI-524 Synagis®
		L	
106	AAA		
K	MEDI-524 Synagis®		

Fig. 5B

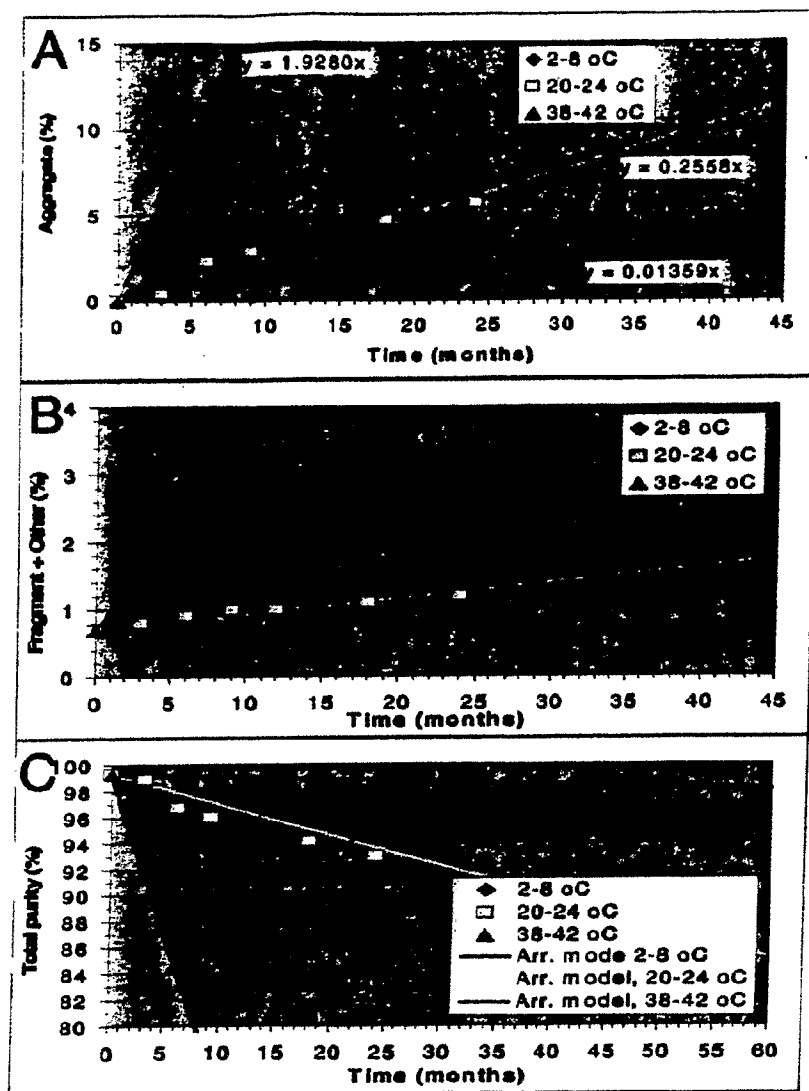


Fig. 6

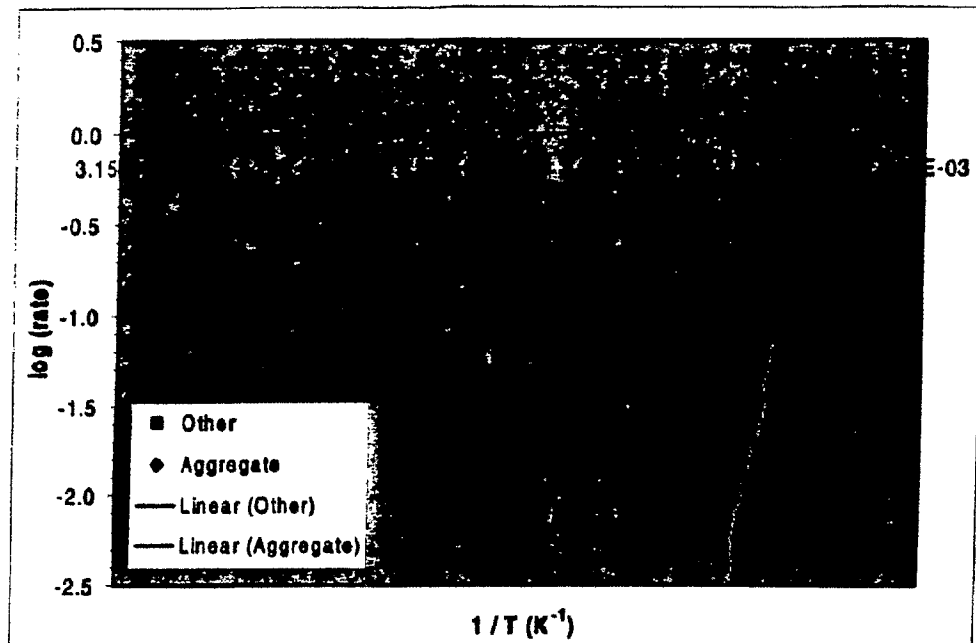


FIG. 7



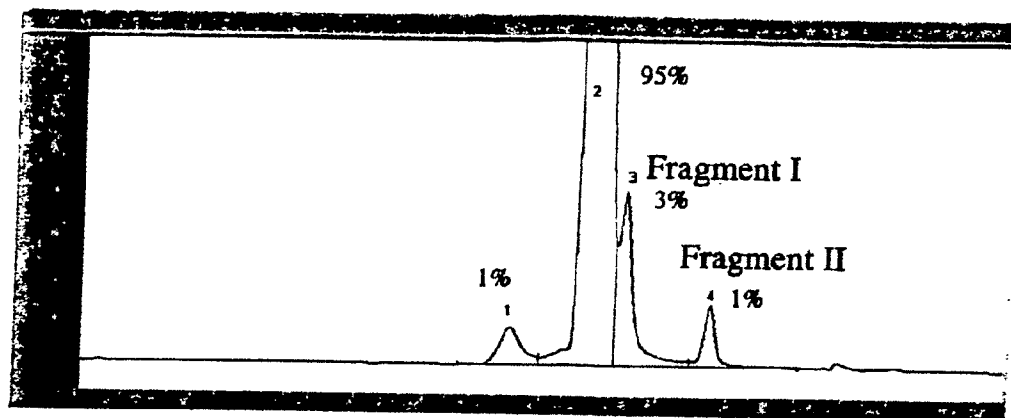


Fig. 8

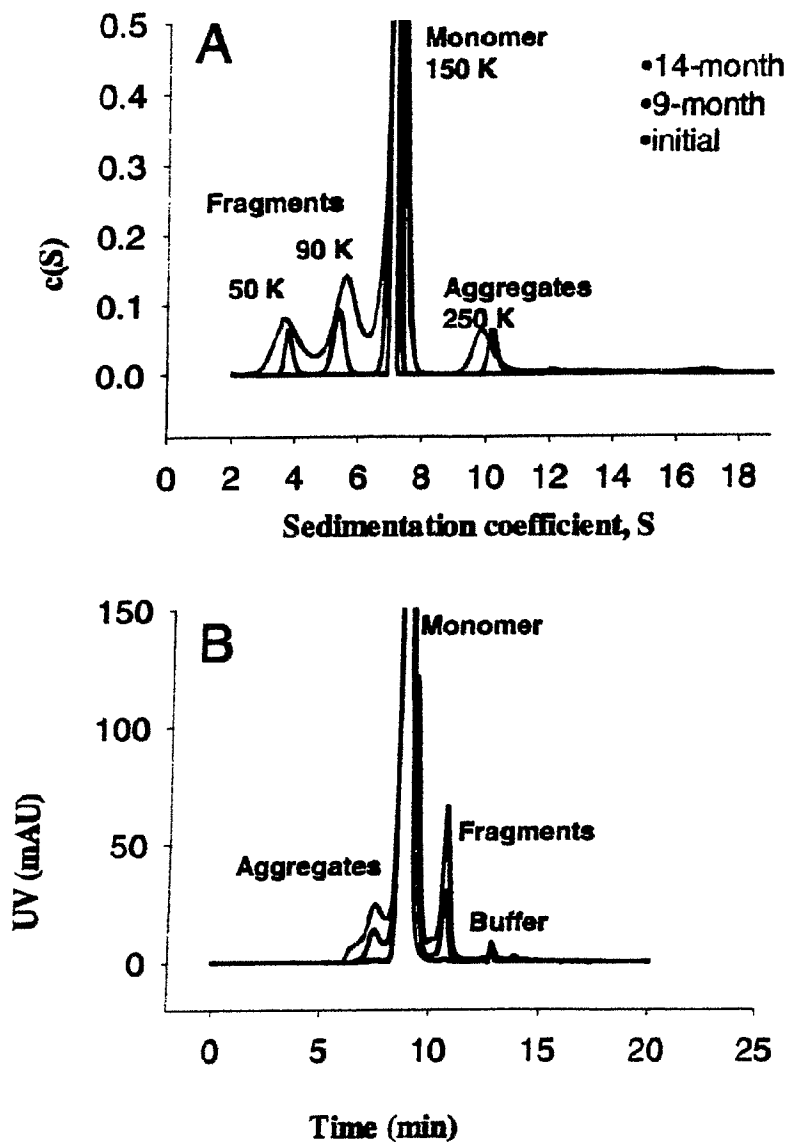


Fig. 9

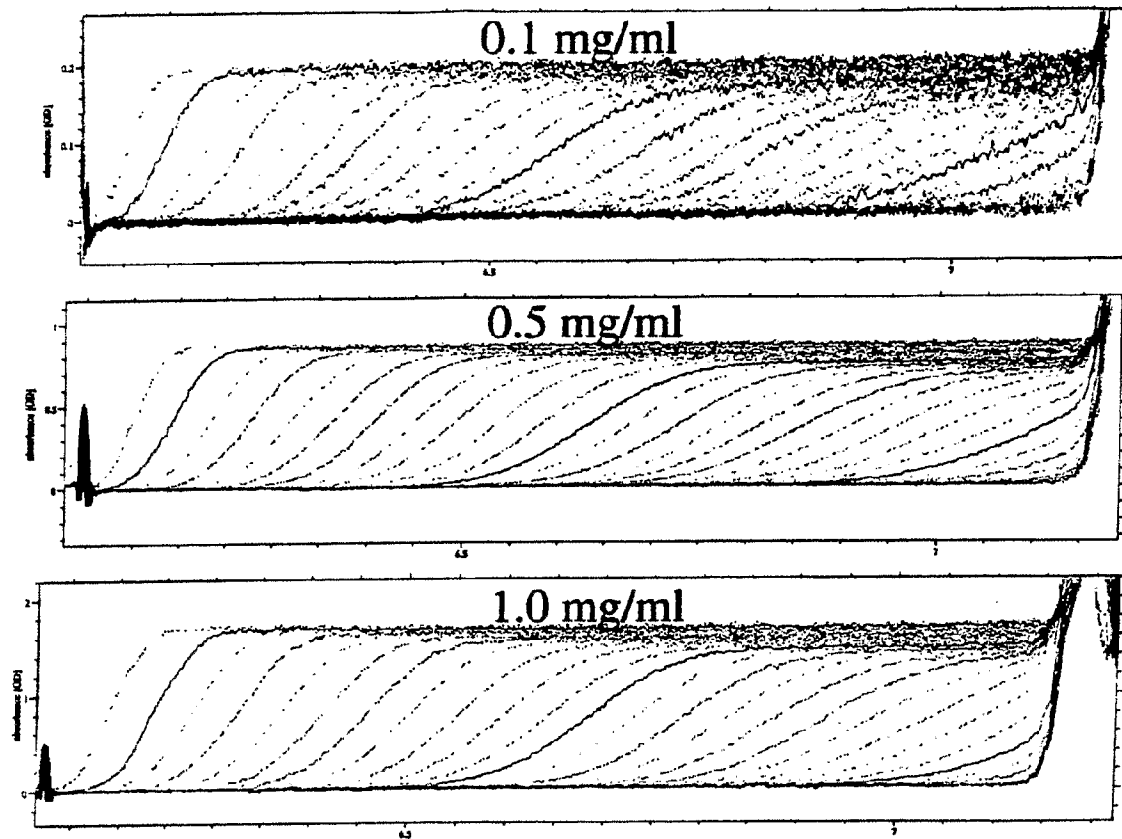


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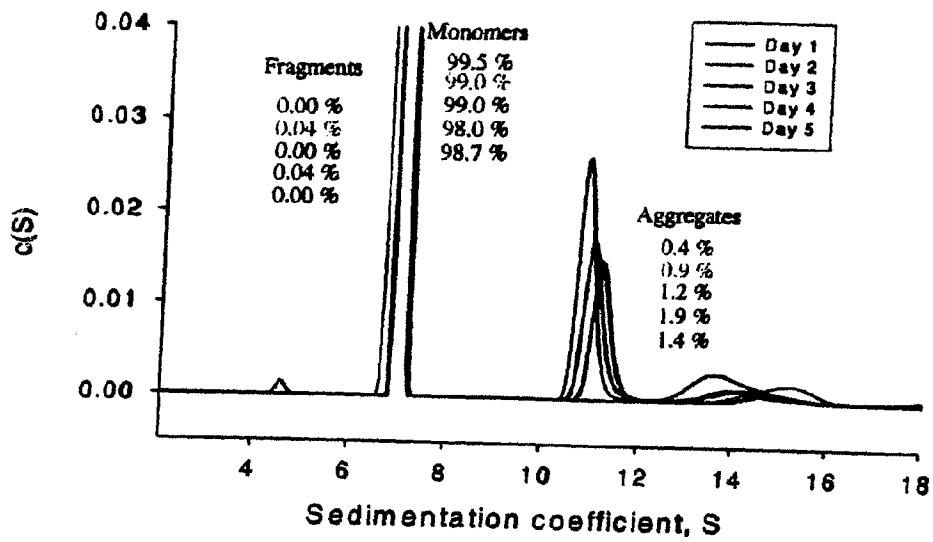


Fig. 11

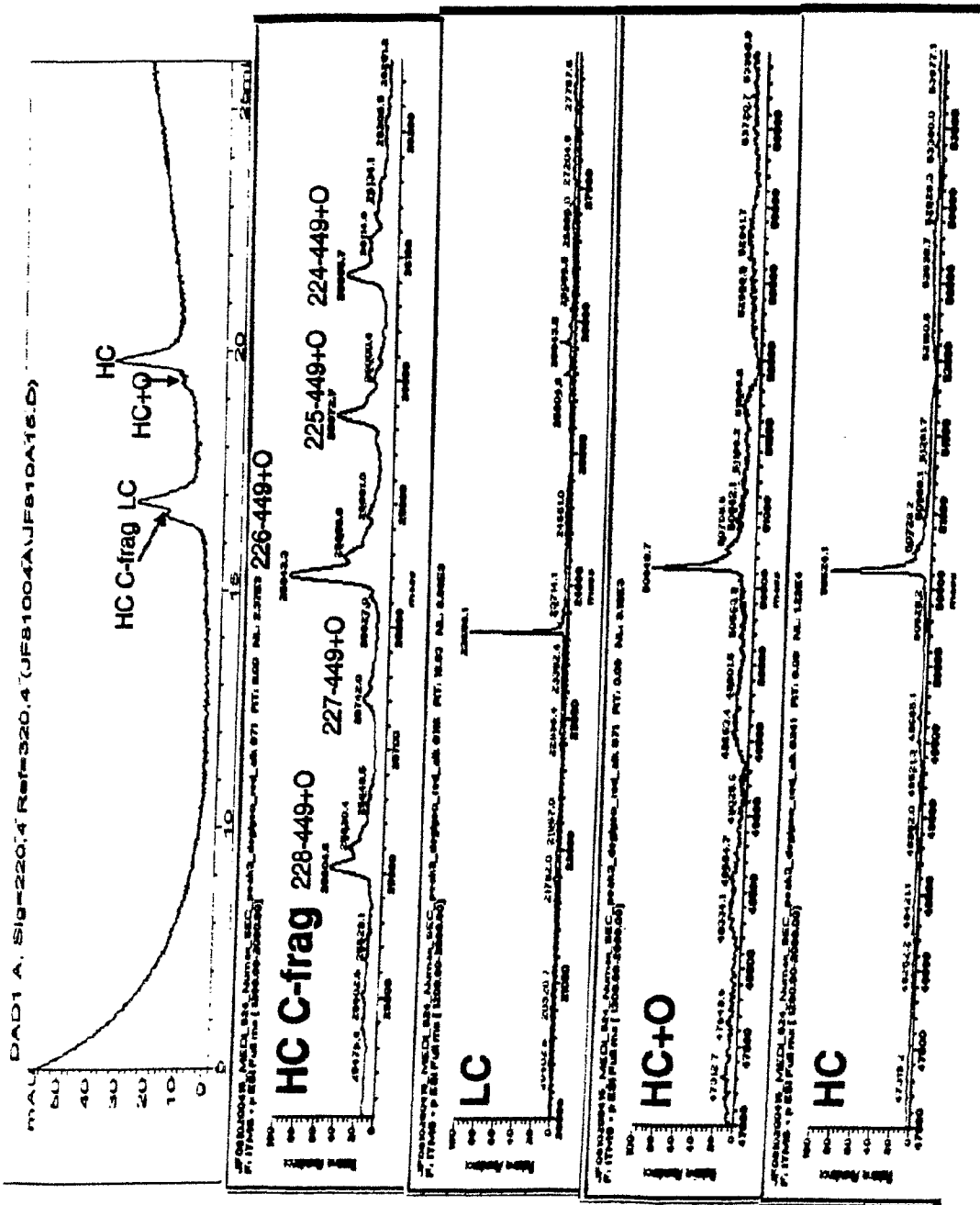
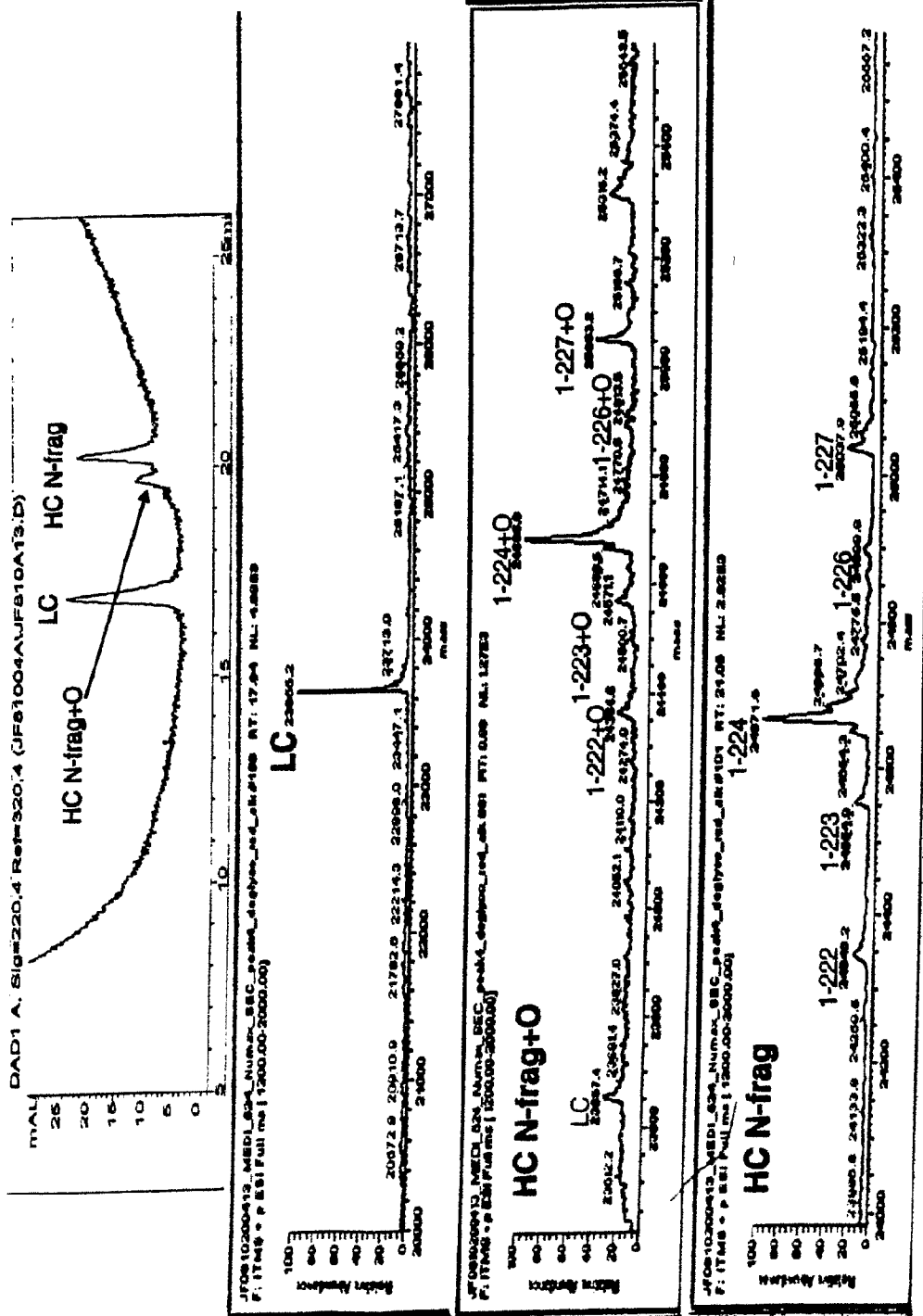


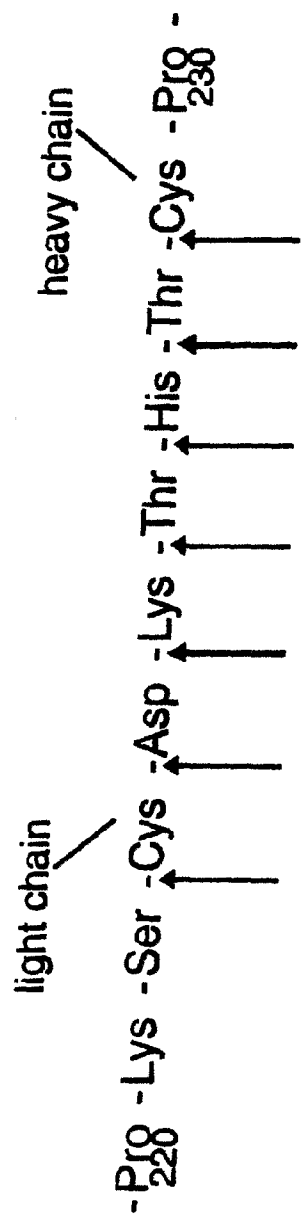
Fig. 12



F16. 13

# Fragmentation Pattern of A4B4L1FR-S28R

(A)



(B)

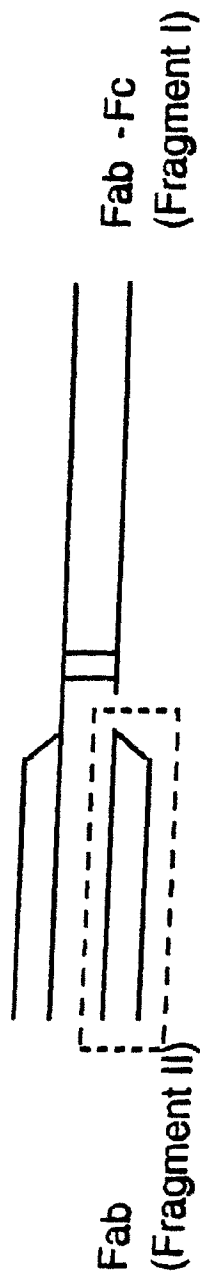


Fig. 14

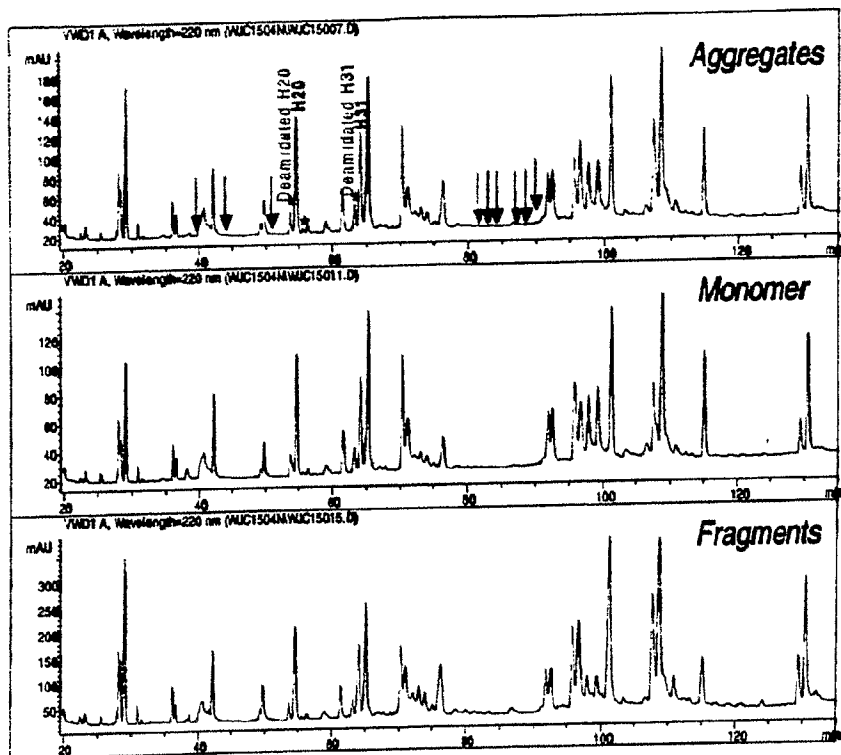


FIG. 15



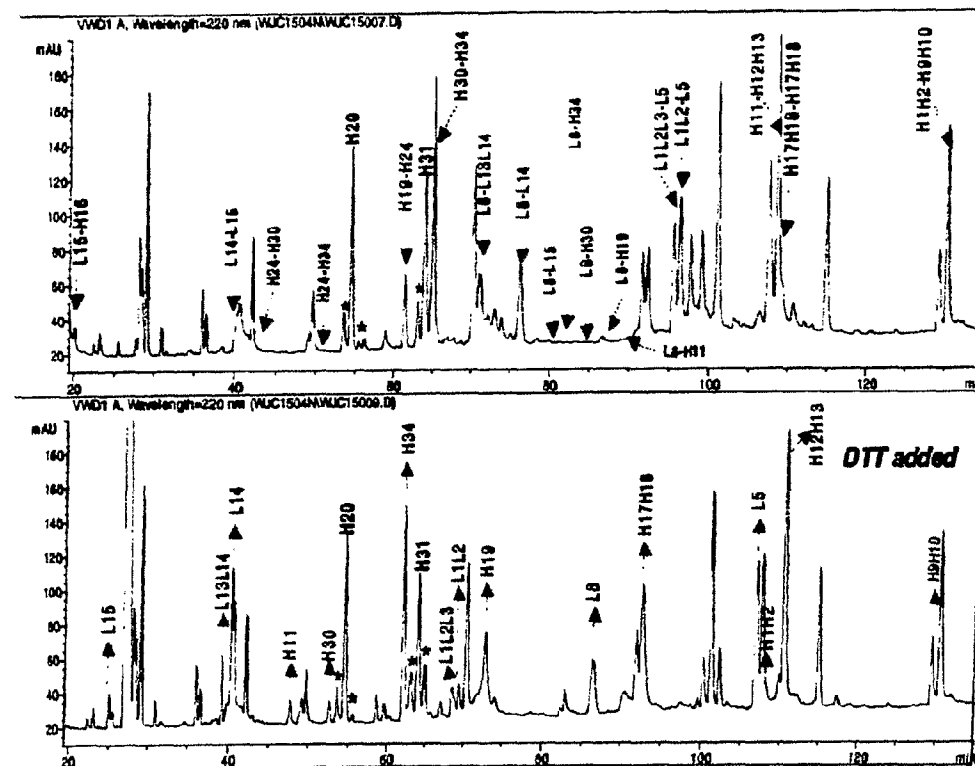


FIG. 16

Fig. 17

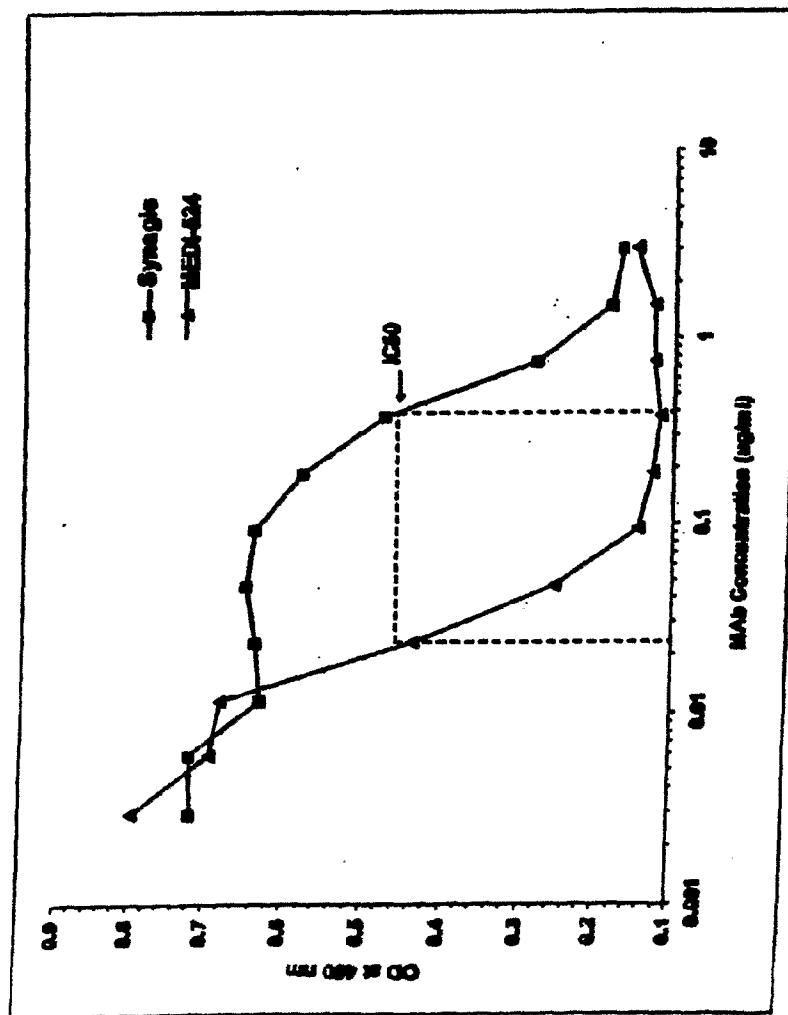
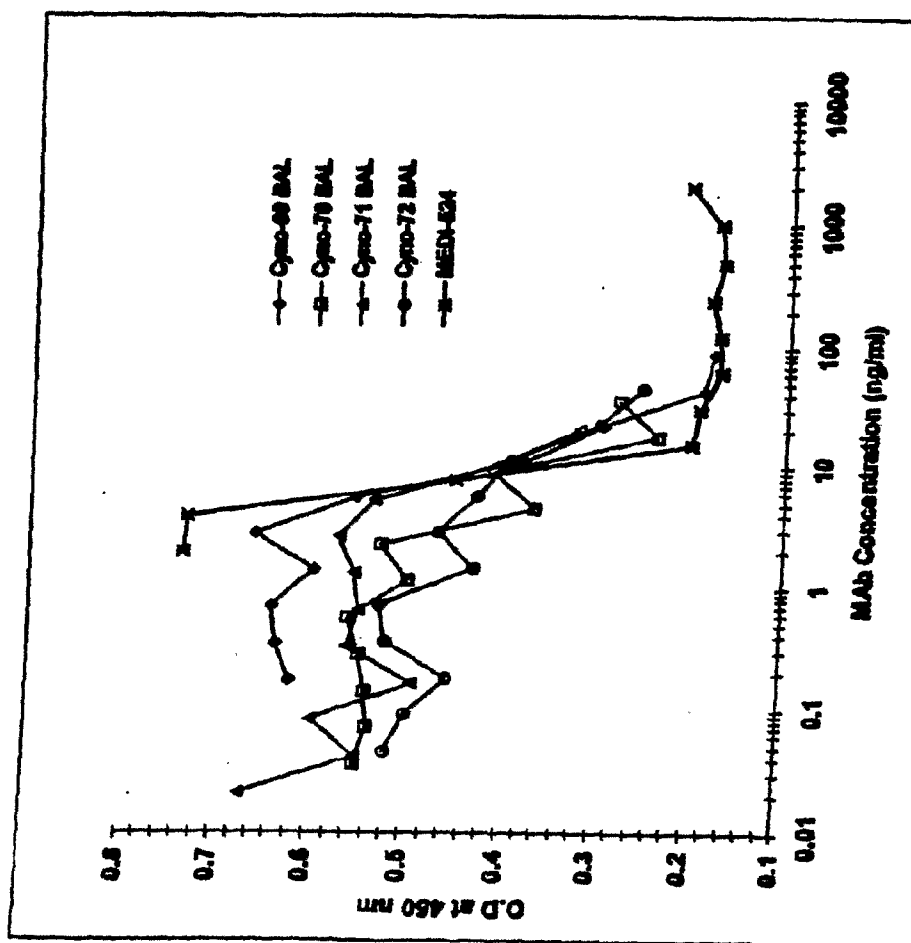
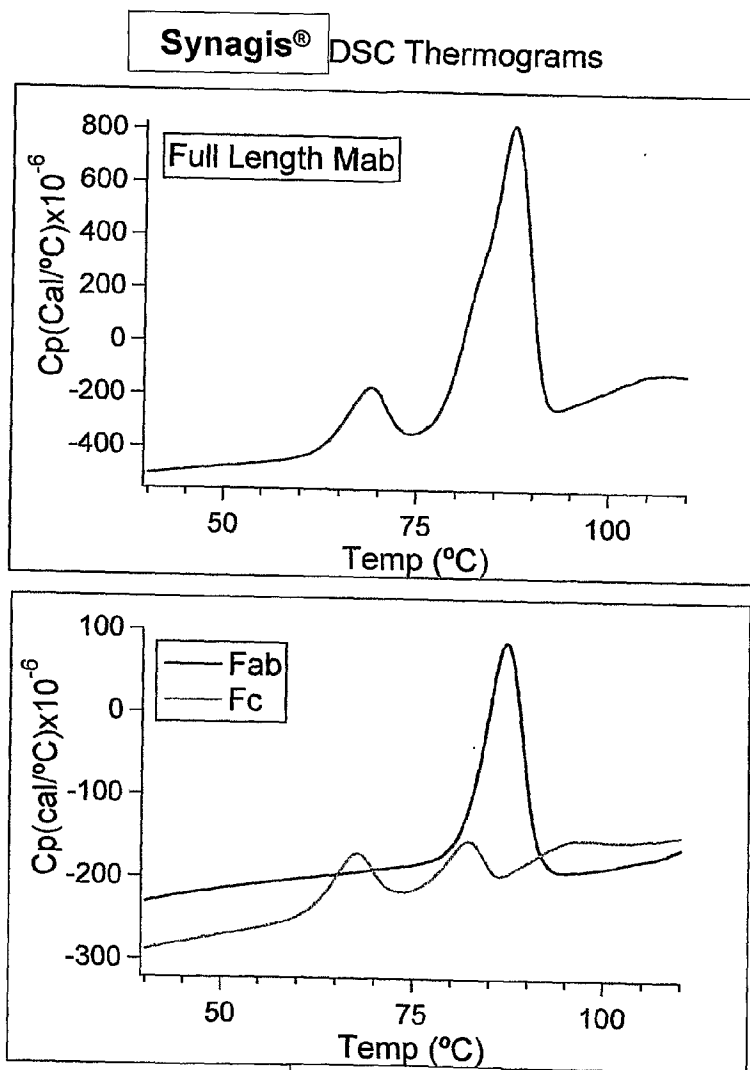


Fig. 18



**Fig. 19**

Jenny Wolford-Formulation

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# Fab T<sub>m</sub> (Bars) and pI

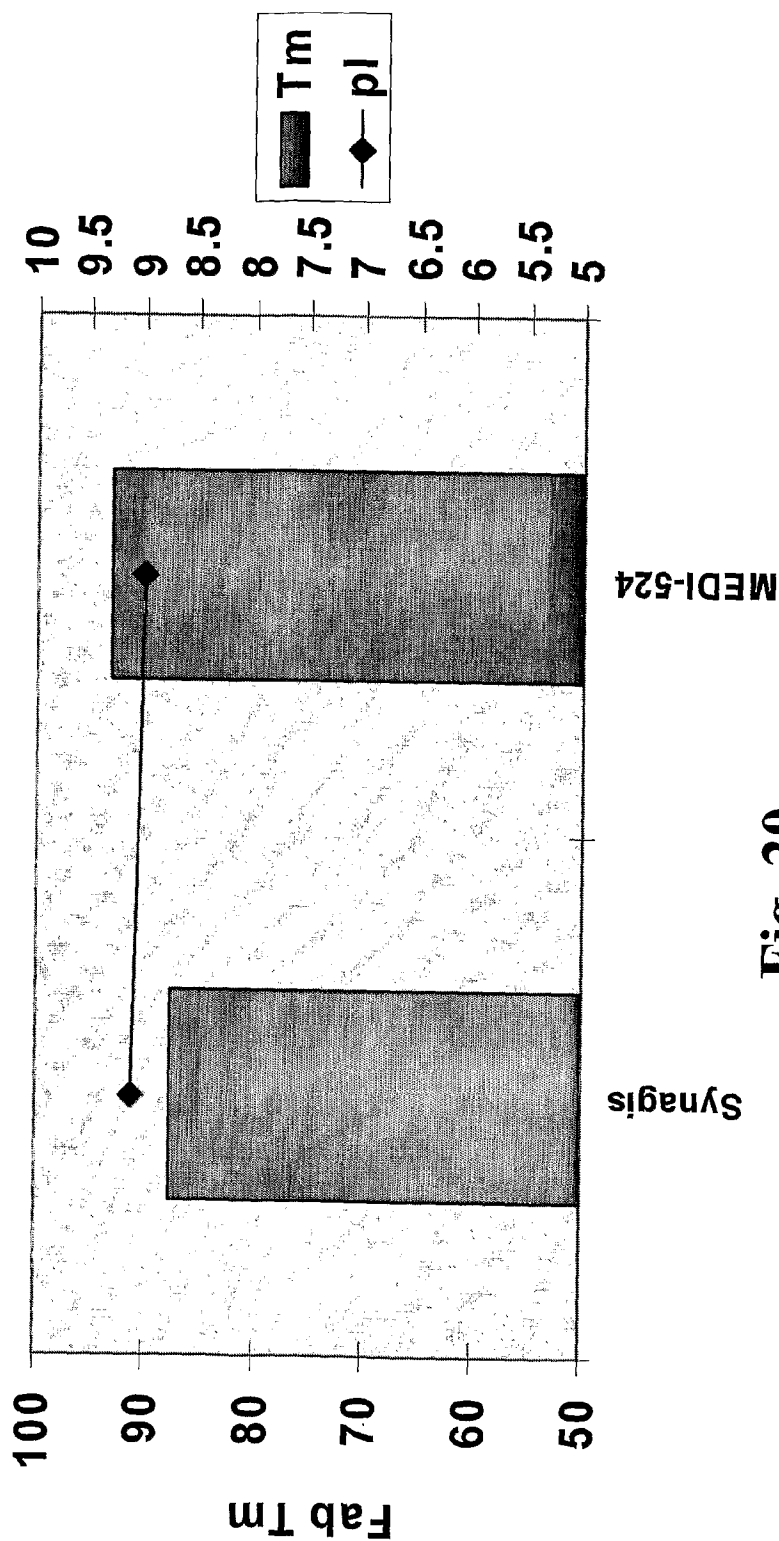


Fig. 20

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10271-170-228

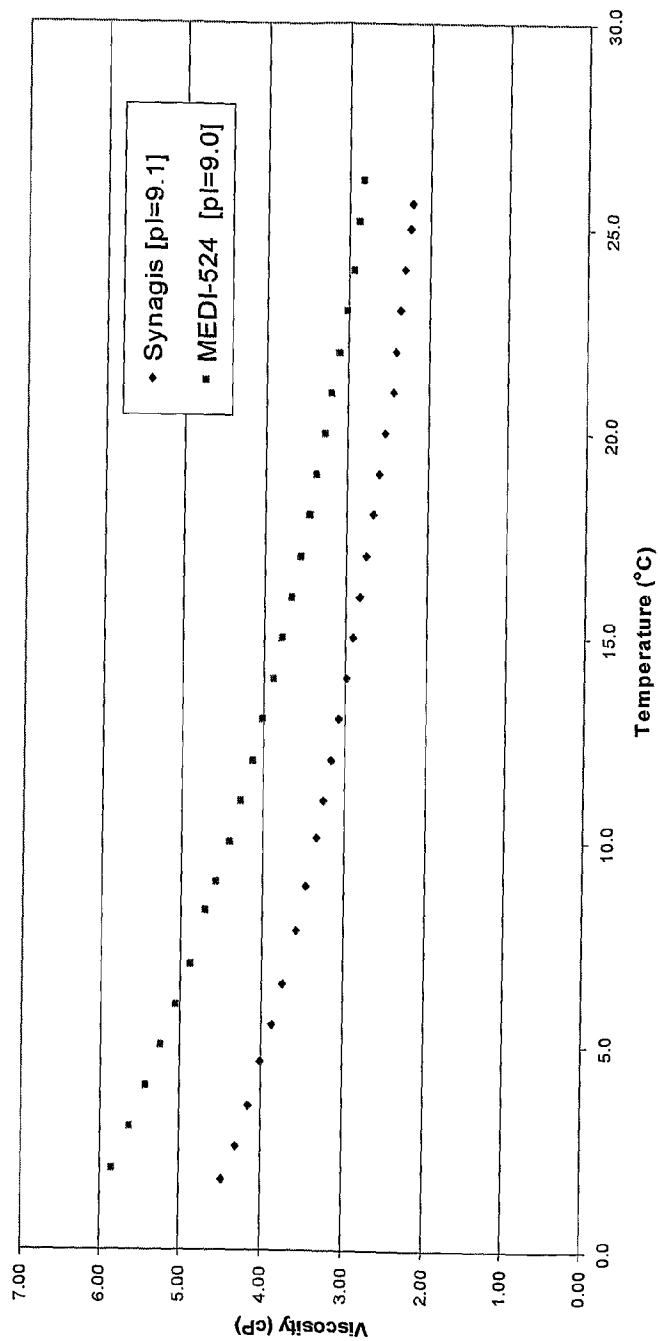
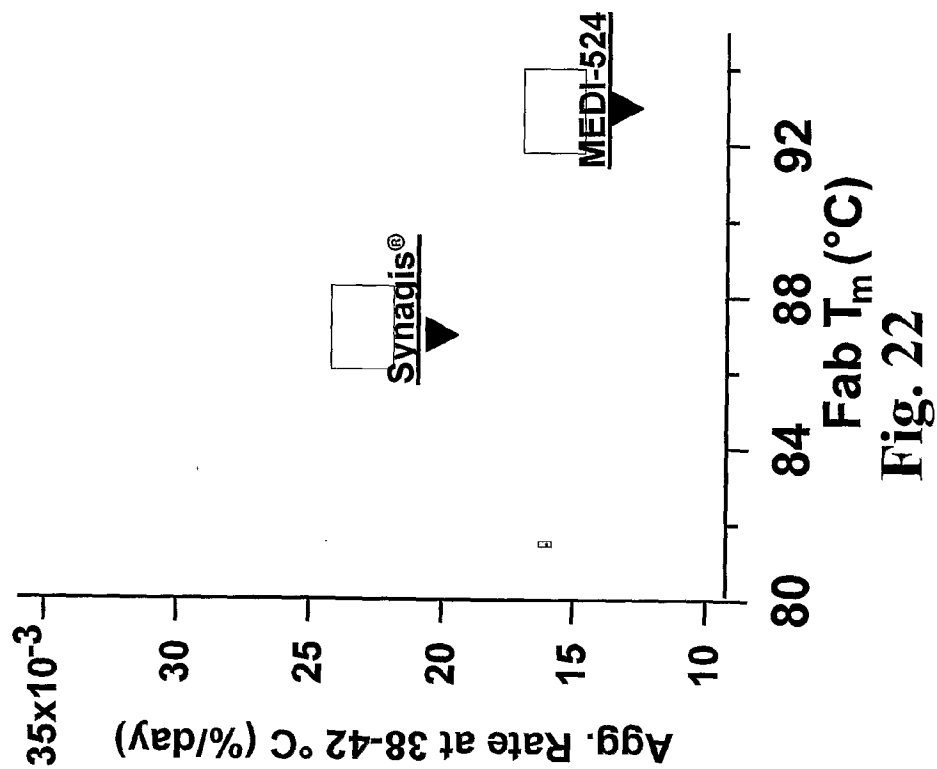


Fig. 21

Sheet 23 of 23



10271-170-228

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 1 5 10  
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 <213> Murine  
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 1 5 10  
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 <213> Murine



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 1 5

&lt;210&gt; 6

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Murine

&lt;400&gt; 6

Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 1 5

&lt;210&gt; 7

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 7

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120

&lt;210&gt; 8

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;221&gt; misc\_feature

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 8

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 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Lys Cys Gln Leu Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr

85 90 95  
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys  
100 105

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<212> PRT  
<213> Artificial Sequence

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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
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<220>  
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1 5

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<211> 106  
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<213> Artificial Sequence

<220>  
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1 5 10 15  
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
20 25 30  
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45  
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

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 substitutions

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<210> 13  
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 <212> PRT  
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<220>  
 <223> Humanized antibody - VL Domain

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 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Phe Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 14  
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<210> 15  
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<220>  
 <223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 15  
 Asp Thr Phe Lys Leu Ala Ser  
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<210> 16  
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 <223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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 Phe Gln Phe Ser Gly Tyr Pro Phe Thr  
 1 5

<210> 17  
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 <212> PRT  
 <213> Artificial Sequence

<220>  
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 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120

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 1 5 10 15

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 substitutions

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 Asp Met Ile Phe Asn Phe Tyr Phe Asp Val  
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 <213> Artificial Sequence

<220>  
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 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
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 100 105

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<210> 23

<211> 7

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1 5

<210> 24

<211> 120

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1				5				10						15	
Thr	Leu	Thr	Leu	Thr	Cys	Thr	Phe	Ser	Gly	Phe	Ser	Leu	Ser	Thr	Pro
			20					25					30		
Gly	Met	Ser	Val	Gly	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Ala	Leu	Glu
		35				40						45			
Trp	Leu	Ala	Asp	Ile	Trp	Trp	Asp	Gly	Lys	Lys	His	Tyr	Asn	Pro	Ser
	50					55					60				
Leu	Lys	Asp	Arg	Leu	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Lys	Asn	Gln	Val
65					70					75				80	
Val	Leu	Lys	Val	Thr	Asn	Met	Asp	Pro	Ala	Asp	Thr	Ala	Thr	Tyr	Tyr
				85					90					95	
Cys	Ala	Arg	Asp	Met	Ile	Phe	Asn	Phe	Tyr	Phe	Asp	Val	Trp	Gly	Gln
			100					105						110	
Gly	Thr	Thr	Val	Thr	Val	Ser	Ser								
			115				120								

<210> 25

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&lt;210&gt; 26

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 26

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 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Arg Gly Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

&lt;210&gt; 27

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

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 antibody and further modified by amino acid  
 substitutions

&lt;400&gt; 27

Asp Thr Arg Gly Leu Pro Ser  
 1 5

&lt;210&gt; 28

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 28

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 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val

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65          70          75          80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85          90          95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
          100          105          110
Gly Thr Thr Val Thr Val Ser Ser
          115          120

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<400> 29
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<220>  
 <223> Humanized antibody - VL Domain

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          20          25          30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35          40          45
Asp Thr Met Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50          55          60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65          70          75          80
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          85          90          95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105

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 substitutions

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<220>

<223> Humanized antibody - VH Domain

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 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120

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<223> Humanized antibody - VL Domain

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 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100

105

&lt;210&gt; 35

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 35

Asp Thr Phe Lys Leu Ser Ser

1

5

&lt;210&gt; 36

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 36

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln

1

5

10

15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala

20

25

30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu

35

40

45

Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Asp Tyr Asn Pro Ser

50

55

60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val

65

70

75

80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr

85

90

95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln

100

105

110

Gly Thr Thr Val Thr Val Ser Ser

115

120

&lt;210&gt; 37

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 37

Asp Ile Trp Trp Asp Gly Lys Lys Asp Tyr Asn Pro Ser Leu Lys Asp

1

5

10

15

&lt;210&gt; 38

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 38

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
          20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35           40           45
Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100           105

```

&lt;210&gt; 39

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 39

```

Ser Ala Ser Ser Arg Val Gly Tyr Met His
1           5           10

```

&lt;210&gt; 40

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 40

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Ser Tyr Asn Pro Ser
          50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85           90           95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
          100           105           110
Gly Thr Thr Val Thr Val Ser Ser
          115           120

```

&lt;210&gt; 41

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 41

Asp	Ile	Trp	Trp	Asp	Gly	Lys	Lys	Ser	Tyr	Asn	Pro	Ser	Leu	Lys	Asp
1				5					10					15	

&lt;210&gt; 42

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 42

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly
1			5						10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Ser	Leu	Ser	Ser	Arg	Val	Gly	Tyr	Met
		20					25					30			
His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr
		35					40					45			
Asp	Thr	Met	Tyr	Gln	Ser	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser
		50				55					60				
Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Asp
65					70				75					80	
Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Phe	Gln	Gly	Ser	Gly	Tyr	Pro	Phe	Thr
			85						90					95	
Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys						
			100					105							

&lt;210&gt; 43

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 43

Asp	Thr	Met	Tyr	Gln	Ser	Ser
1				5		

&lt;210&gt; 44

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 44

Gln	Val	Thr	Leu	Arg	Glu	Ser	Gly	Pro	Ala	Leu	Val	Lys	Pro	Thr	Gln
1				5					10					15	

```

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20                25                30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35                40                45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser
      50                55                60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
      65                70                75                80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85                90                95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
      100                105                110
Gly Thr Thr Val Thr Val Ser Ser
      115                120

```

<210> 45  
 <211> 16  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

```

<400> 45
Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser Leu Lys Asp
1           5           10           15

```

<210> 46  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

```

<400> 46
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Leu Pro Ser Ser Arg Val Gly Tyr Met
      20                25                30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35                40                45
Asp Thr Met Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50                55                60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
      65                70                75                80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85                90                95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100                105

```

<210> 47  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid

## substitutions

&lt;400&gt; 47

Leu Pro Ser Ser Arg Val Gly Tyr Met His  
 1 5 10

&lt;210&gt; 48

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 48

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120

&lt;210&gt; 49

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 49

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

&lt;210&gt; 50

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 50

Asp Thr Phe Phe Leu Asp Ser  
1 5

&lt;210&gt; 51

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Domain

&lt;400&gt; 51

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15  
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser  
50 55 60  
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
100 105 110  
Gly Thr Thr Val Thr Val Ser Ser  
115 120

&lt;210&gt; 52

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 52

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
1 5 10 15  
Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met  
20 25 30  
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
35 40 45  
Asp Thr Arg Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
50 55 60  
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
65 70 75 80  
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
85 90 95  
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

&lt;210&gt; 53

&lt;211&gt; 7

<212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

<400> 53  
 Asp Thr Arg Tyr Gln Ser Ser  
 1 5

<210> 54  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

<400> 54  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 55  
 <211> 120  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Domain

<400> 55  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120



<210> 56  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

<400> 56  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 57  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

<400> 57  
 Asp Thr Tyr Lys Gln Thr Ser  
 1 5

<210> 58  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

<400> 58  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Arg Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100

105

&lt;210&gt; 59

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 59

Asp Thr Arg Tyr Leu Ser Ser

1

5

&lt;210&gt; 60

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 60

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly

1

5

10

15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met

20

25

30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr

35

40

45

Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser

50

55

60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp

65

70

75

80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Phe Tyr Pro Phe Thr

85

90

95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100

105

&lt;210&gt; 61

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 61

Phe Gln Gly Ser Phe Tyr Pro Phe Thr

1

5

&lt;210&gt; 62

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 62

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Phe Lys Leu Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
           100           105

```

&lt;210&gt; 63

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 63

```

Asp Thr Phe Lys Leu Thr Ser
1           5

```

&lt;210&gt; 64

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 64

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
           100           105

```

&lt;210&gt; 65

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Humanized antibody - VL Domain

<400> 65

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Phe Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
           100           105

```

<210> 66

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 66

```

Asp Thr Phe Arg Leu Ala Ser
1           5

```

<210> 67

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VH Domain

<400> 67

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
           20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
           35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser
           50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
           85           90           95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
           100           105           110
Gly Thr Thr Val Thr Val Ser Ser
           115           120

```

<210> 68

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VL Domain

<400> 68

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Tyr Arg His Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
           100           105

```

<210> 69

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 69

```

Asp Thr Tyr Arg His Ser Ser
1           5

```

<210> 70

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VL Domain

<400> 70

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Tyr Lys Gln Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
           100           105

```

<210> 71

<211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

<400> 71  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Phe His Arg Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 72  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

<400> 72  
 Ser Leu Ser Ser Ser Val Gly Tyr Met His  
 1 5 10

<210> 73  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

<400> 73  
 Asp Thr Phe Phe His Arg Ser  
 1 5

<210> 74  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

<400> 74

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Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
          20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35           40           45
Asp Thr Leu Leu Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100           105

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&lt;210&gt; 75

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 75

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Asp Thr Leu Leu Leu Asp Ser
1           5

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&lt;210&gt; 76

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 76

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Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
          20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35           40           45
Asp Thr Ser Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100           105

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&lt;210&gt; 77

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal

antibody and further modified by amino acid  
substitutions

<400> 77

Asp Thr Ser Phe Leu Asp Ser  
1 5

<210> 78

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VH Domain

<400> 78

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110  
Gly Thr Thr Val Thr Val Ser Ser  
115 120

<210> 79

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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Asp Met Ile Thr Asn Phe Tyr Phe Asp Val  
1 5 10

<210> 80

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 80

Lys Cys Gln Ser Ser Val Gly Tyr Met His  
1 5 10



<210> 81  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 81  
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1 5

<210> 82  
<211> 16  
<212> PRT  
<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 82  
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1 5 10 15

<210> 83  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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Asp Met Ile Thr Asn Trp Tyr Phe Asp Val  
1 5 10

<210> 84  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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1 5 10

<210> 85  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>

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<400> 85

Asp Thr Ser Tyr Leu Ser Ser  
1 5

<210> 86

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 86

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1 5 10 15

<210> 87

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 87

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<210> 88

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 88

Asp Thr Lys Lys Leu Ser Ser  
1 5

<210> 89

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 89

Lys Leu Gln Leu Ser Val Gly Tyr Met His  
1 5 10

&lt;210&gt; 90

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 90

Asp Thr Phe Tyr Leu Ser Ser  
1 5

&lt;210&gt; 91

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 91

Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser Leu Lys Ser  
1 5 10 15

&lt;210&gt; 92

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 92

Lys Leu Gln Ser Ser Val Gly Tyr Met His  
1 5 10

&lt;210&gt; 93

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 93

Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser Leu Lys Ser  
1 5 10 15

<210> 94  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 94  
Ser Met Ile Phe Asn Trp Tyr Phe Asp Val  
1 5 10

<210> 95  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 95  
Lys Leu Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 96  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 96  
Asp Thr Phe Lys Leu Ser Ser  
1 5

<210> 97  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 97  
Ser Met Ile Phe Asn Phe Tyr Phe Asp Val  
1 5 10

<210> 98  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 98

Lys Leu Gln Leu Arg Val Gly Tyr Met His  
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<210> 99

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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<210> 100

<211> 16

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 100

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<210> 101

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 101

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<210> 102

<211> 7

<212> PRT

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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1 5

<210> 103

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 103

Asp Ile Trp Trp Asp Gly Lys Lys Asp Tyr Asn Pro Ser Leu Lys Asp  
1 5 10 15

<210> 104

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 104

Lys Leu Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 105

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 105

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1 5

<210> 106

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 106

Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser Leu Lys Ser  
1 5 10 15

<210> 107  
<211> 10  
<212> PRT  
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<220>  
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antibody and further modified by amino acid  
substitutions

<400> 107  
Lys Leu Ser Ser Arg Val Gly Tyr Met His  
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<210> 108  
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antibody and further modified by amino acid  
substitutions

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<210> 109  
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antibody and further modified by amino acid  
substitutions

<400> 109  
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1 5 10 15

<210> 110  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 110  
Lys Leu Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 111  
<211> 16  
<212> PRT  
<213> Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 111

Asp	Ile	Trp	Trp	Asp	Asp	Lys	Lys	Ser	Tyr	Asn	Pro	Ser	Leu	Lys	Asp
1				5					10					15	

&lt;210&gt; 112

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 112

Lys	Cys	Ser	Leu	Ser	Val	Gly	Tyr	Met	His
1				5					10

&lt;210&gt; 113

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 113

Asp	Thr	Arg	Lys	Leu	Ala	Ser
1				5		

&lt;210&gt; 114

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 114

Asp	Ile	Trp	Trp	Asp	Gly	Lys	Lys	Ser	Tyr	Asn	Pro	Ser	Leu	Lys	Ser
1				5					10					15	

&lt;210&gt; 115

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions



<400> 115

Lys Cys Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 116

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

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antibody and further modified by amino acid  
substitutions

<400> 116

Asp Thr Arg Gly Leu Ala Ser  
1 5

<210> 117

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 117

Lys Cys Ser Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 118

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 118

Asp Thr Arg Lys Leu Pro Ser  
1 5

<210> 119

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 119

Lys Cys Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 120  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
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antibody and further modified by amino acid  
substitutions

<400> 120  
Ser Leu Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 121  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 121  
Asp Thr Met Lys Leu Ala Ser  
1 5

<210> 122  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 122  
Ser Leu Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 123  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 123  
Asp Thr Ser Arg Leu Ala Ser  
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<210> 124  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 124

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1 5

<210> 125

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 125

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1 5 10

<210> 126

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 126

Asp Thr Ser Leu Leu Asp Ser  
1 5

<210> 127

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 127

Ser Cys Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 128

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 128  
Asp Thr Ser Lys Leu Asp Ser  
1 5

<210> 129  
<211> 10  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 129  
Ser Cys Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 130  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 130  
Ser Cys Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 131  
<211> 7  
<212> PRT  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 131  
Asp Thr Leu Lys Leu Asp Ser  
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<210> 132  
<211> 10  
<212> PRT  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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Ser Cys Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 133  
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<220>  
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<210> 134  
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<210> 135  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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1 5 10

<210> 137  
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<212> PRT  
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<400> 137

Asp Thr Ser Lys Leu Ser Ser  
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<210> 138

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 138

Ser Leu Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 139

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 139

Asp Thr Ser Lys Gln Ala Ser  
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<210> 140

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 140

Ser Leu Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 141

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid

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&lt;400&gt; 141

Asp Thr Ser Lys Gln Ser Ser  
1 5

&lt;210&gt; 142

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 142

Ser Cys Ser Leu Ser Val Gly Tyr Met His  
1 5 10

&lt;210&gt; 143

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 143

Asp Thr Ser Tyr Leu Ala Ser  
1 5

&lt;210&gt; 144

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 144

Ser Cys Ser Ser Ser Val Gly Tyr Met His  
1 5 10

&lt;210&gt; 145

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 145

Asp Thr Ser Tyr Leu Ser Ser  
1 5

<210> 146  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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Ser Cys Ser Ser Arg Val Gly Tyr Met His  
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<210> 147  
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<220>  
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<400> 147  
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<210> 148  
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<220>  
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<400> 148  
Ser Cys Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 149  
<211> 7  
<212> PRT  
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<400> 149  
Asp Thr Ser Tyr Gln Ser Ser  
1 5

<210> 150  
<211> 10  
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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 150

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<210> 151

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 151

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<210> 152

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 152

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<210> 153

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 153

Lys Pro Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 154

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 154

Asp Thr Met Lys Gln Ala Ser  
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<210> 155

<211> 10

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 155

Lys Pro Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 156

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 156

Asp Thr Met Lys Gln Ser Ser  
1 5

<210> 157

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 157

Lys Pro Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 158

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 158

Asp Thr Met Tyr Leu Ala Ser  
1 5

<210> 159  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 159  
Lys Pro Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 160  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 160  
Asp Thr Met Tyr Leu Ser Ser  
1 5

<210> 161  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 161  
Lys Pro Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 162  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 162  
Asp Thr Met Lys Leu Ala Ser  
1 5

<210> 163  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 163

Lys Pro Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 164

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 164

Asp Thr Met Lys Leu Ser Ser  
1 5

<210> 165

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 165

Asp Thr Ser Lys Leu Ser Ser  
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<210> 166

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 166

Ser Pro Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 167

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid

## substitutions

&lt;400&gt; 167

Asp Thr Arg Tyr Gln Ala Ser

1

5

&lt;210&gt; 168

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 168

Ser Pro Ser Ser Ser Val Gly Tyr Met His

1

5

10

&lt;210&gt; 169

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 169

Ser Pro Ser Leu Ser Val Gly Tyr Met His

1

5

10

&lt;210&gt; 170

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 170

Asp Thr Arg Tyr Gln Ala Ser

1

5

&lt;210&gt; 171

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 171

Ser Pro Gln Ser Arg Val Gly Tyr Met His

1

5

10

<210> 172  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 172  
Asp Thr Arg Lys Gln Ser Ser  
1 5

<210> 173  
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<212> PRT  
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<220>  
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antibody and further modified by amino acid  
substitutions

<400> 173  
Ser Pro Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 174  
<211> 7  
<212> PRT  
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<220>  
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antibody and further modified by amino acid  
substitutions

<400> 174  
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1 5

<210> 175  
<211> 7  
<212> PRT  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 175  
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1 5

<210> 176  
<211> 10  
<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 176

Ser Pro Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 177

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 177

Ser Pro Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 178

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 178

Asp Thr Arg Tyr Leu Ala Ser  
1 5

<210> 179

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 179

Lys Ala Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 180

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 180

Lys Ala Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 181

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 181

Lys Ala Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 182

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 182

Lys Ala Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 183

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 183

Lys Ala Ser Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 184

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions



<400> 184

Lys Ala Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 185

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 185

Lys Ala Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 186

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 186

Lys Ala Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 187

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 187

Ser Ala Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 188

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 188

Ser Ala Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 189  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 189  
Ser Ala Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 190  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 190  
Ser Ala Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 191  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 191  
Ser Ala Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 192  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 192  
Leu Pro Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 193  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 193

Leu Pro Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 194

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 194

Leu Pro Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 195

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 195

Leu Cys Ser Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 196

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 196

Leu Cys Ser Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 197

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 197

Leu Cys Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 198

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 198

Leu Cys Ser Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 199

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 199

Leu Pro Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 200

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 200

Leu Pro Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 201

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 201

Leu Pro Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 202

<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 202  
Leu Pro Gln Leu Arg Val Gly Tyr Met His  
1 5 10

<210> 203  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 203  
Leu Cys Gln Ser Arg Val Gly Tyr Met His  
1 5 10

<210> 204  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 204  
Leu Cys Gln Leu Ser Val Gly Tyr Met His  
1 5 10

<210> 205  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 205  
Leu Cys Gln Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 206  
<211> 10  
<212> PRT  
<213> Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 206

Leu Cys Gln Leu Arg Val Gly Tyr Met His  
1 5 10

&lt;210&gt; 207

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 207

Ser Ala Gln Leu Ser Val Gly Tyr Met His  
1 5 10

&lt;210&gt; 208

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 208

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15  
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
50 55 60  
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala  
100 105 110  
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
115 120 125  
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140  
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
145 150 155 160  
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
165 170 175  
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
180 185 190  
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
195 200 205  
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

&lt;210&gt; 209

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 209

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Lys Cys Gln Leu Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser

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                165                170                175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
                180                185                190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
                195                200                205
Asn Arg Gly Glu Cys
                210

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&lt;210&gt; 210

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 210

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Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1          5          10          15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20          25          30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35          40          45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
          50          55          60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
          65          70          75          80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85          90          95
Cys Ala Arg Ser Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln
          100          105          110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
          115          120          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
          130          135          140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
          145          150          155          160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
          165          170          175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
          180          185          190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
          195          200          205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
          210          215          220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
          225          230          235          240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
          245          250          255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
          260          265          270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
          275          280          285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
          290          295          300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
          305          310          315          320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
          325          330          335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
          340          345          350

```



Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
           355                          360                          365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
           370                          375                          380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385                          390                          395                          400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
           405                          410                          415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
           420                          425                          430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
           435                          440                          445  
 Gly Lys  
           450

<210> 211  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Chain

<400> 211  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1                          5                          10                          15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
           20                          25                          30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
           35                          40                          45  
 Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
           50                          55                          60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65                          70                          75                          80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Phe Ser Gly Tyr Pro Phe Thr  
           85                          90                          95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
           100                          105                          110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
           115                          120                          125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
           130                          135                          140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145                          150                          155                          160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
           165                          170                          175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
           180                          185                          190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
           195                          200                          205  
 Asn Arg Gly Glu Cys  
           210

<210> 212  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

&lt;400&gt; 212

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

&lt;210&gt; 213

<211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> Humanized antibody - VL Chain

<400> 213

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met
          20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35           40           45
Asp Thr Phe Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
          65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
          115          120          125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
          130          135          140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
          145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
          165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
          180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
          195          200          205
Asn Arg Gly Glu Cys
          210

```

<210> 214  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> Humanized antibody - VH Chain

<400> 214

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro
          20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser
          50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
          65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85           90           95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
          100          105          110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val

```

```

      115              120              125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130              135              140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145              150              155              160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165              170              175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180              185              190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195              200              205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
      210              215              220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225              230              235              240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
      245              250              255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
      260              265              270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
      275              280              285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
      290              295              300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305              310              315              320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
      325              330              335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
      340              345              350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
      355              360              365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
      370              375              380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385              390              395              400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
      405              410              415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
      420              425              430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
      435              440              445
Gly Lys
      450

```

```

<210> 215
<211> 213
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VL Chain

```

```

<400> 215
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35      40      45
Asp Thr Arg Gly Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50      55      60

```

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 216  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 216  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Pro  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

```

                245                250                255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
                260                265                270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                275                280                285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                290                295                300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                310                315                320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                330                335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                340                345                350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                355                360                365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                370                375                380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                390                395                400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                410                415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
                420                425                430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                435                440                445
Gly Lys
                450

```

&lt;210&gt; 217

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 217

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1                5                10                15
Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met
                20                25                30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                35                40                45
Asp Thr Met Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                50                55                60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                70                75                80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                90                95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
                100                105                110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
                115                120                125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                130                135                140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                150                155                160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                170                175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
                180                185                190

```

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 218  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 218  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

```

      370              375              380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385      213      390      395      400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
      405      410      415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
      420      425      430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
      435      440      445
Gly Lys
      450

```

<210> 219  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Chain

```

<400> 219
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35      40      45
Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
      65      70      75      80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
      100      105      110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
      115      120      125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130      135      140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
      145      150      155      160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165      170      175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180      185      190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195      200      205
Asn Arg Gly Glu Cys
      210

```

<210> 220  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

```

<400> 220
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1      5      10      15

```



```

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20      25      30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35      40      45
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Asp Tyr Asn Pro Ser
      50      55      60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
      65      70      75      80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85      90      95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
      100      105      110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115      120      125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130      135      140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
      145      150      155      160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165      170      175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180      185      190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195      200      205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
      210      215      220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
      225      230      235      240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
      245      250      255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
      260      265      270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
      275      280      285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
      290      295      300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
      305      310      315      320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
      325      330      335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
      340      345      350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
      355      360      365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
      370      375      380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
      385      390      395      400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
      405      410      415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
      420      425      430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
      435      440      445
Gly Lys
      450

```

&lt;210&gt; 221

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 221

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
          20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35           40           45
Asp Thr Phe Lys Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
          115          120          125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130          135          140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
          165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
          180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195          200          205
Asn Arg Gly Glu Cys
210

```

&lt;210&gt; 222

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 222

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys Ser Tyr Asn Pro Ser
50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85           90           95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
100          105          110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
          115          120          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130          135          140

```

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

<210> 223

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VL Chain

<400> 223

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Met Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr

```

      85              90              95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
      100              105              110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
      115              120              125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130              135              140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
      145              150              155              160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165              170              175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180              185              190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195              200              205
Asn Arg Gly Glu Cys
      210

```

&lt;210&gt; 224

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 224

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1              5              10              15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20              25              30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35              40              45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser
      50              55              60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
      65              70              75              80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85              90              95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
      100              105              110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115              120              125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130              135              140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
      145              150              155              160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165              170              175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180              185              190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195              200              205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
      210              215              220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
      225              230              235              240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
      245              250              255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

```

```

                260                265                270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                275                280                285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                290                295                300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                310                315                320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                330                335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                340                345                350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                355                360                365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370                375                380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                390                395                400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                410                415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
                420                425                430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                435                440                445
Gly Lys
                450

```

```

<210> 225
<211> 213
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VL Chain

```

```

<400> 225
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1                5                10                15
Asp Arg Val Thr Ile Thr Cys Leu Pro Ser Ser Arg Val Gly Tyr Met
                20                25                30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35                40                45
Asp Thr Met Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50                55                60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                70                75                80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                90                95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
100                105                110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115                120                125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130                135                140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                150                155                160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                170                175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180                185                190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195                200                205

```

Asn Arg Gly Glu Cys  
210

<210> 226  
<211> 450  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Humanized antibody - VH Chain

<400> 226  
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15  
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
50 55 60  
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
65 70 75 80  
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
85 90 95  
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
100 105 110  
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
115 120 125  
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140  
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
145 150 155 160  
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
165 170 175  
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
180 185 190  
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
195 200 205  
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
210 215 220  
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
225 230 235 240  
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
245 250 255  
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
260 265 270  
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
275 280 285  
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
290 295 300  
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
305 310 315 320  
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
325 330 335  
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
340 345 350  
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
355 360 365  
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
370 375 380  
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

```

385          390          395          400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
          405          410          415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
          420          425          430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
          435          440          445
Gly Lys
          450

```

```

<210> 227
<211> 213
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VL Chain

```

```

<400> 227
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1          5          10          15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
          20          25          30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35          40          45
Asp Thr Phe Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50          55          60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
          65          70          75          80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85          90          95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
          115          120          125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
          130          135          140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
          145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
          165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
          180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
          195          200          205
Asn Arg Gly Glu Cys
          210

```

```

<210> 228
<211> 450
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VH Chain

```

```

<400> 228
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1          5          10          15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20          25          30

```

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
           35                          40                          45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser  
           50                          55                          60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65                          70                          75                          80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
           85                          90                          95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
           100                          105                          110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
           115                          120                          125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130                          135                          140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145                          150                          155                          160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
           165                          170                          175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
           180                          185                          190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
           195                          200                          205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210                          215                          220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225                          230                          235                          240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
           245                          250                          255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
           260                          265                          270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
           275                          280                          285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290                          295                          300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305                          310                          315                          320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
           325                          330                          335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
           340                          345                          350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
           355                          360                          365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
           370                          375                          380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385                          390                          395                          400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
           405                          410                          415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
           420                          425                          430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
           435                          440                          445  
 Gly Lys  
           450

<210> 229  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>



<223> Humanized antibody - VL Chain

<400> 229

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met
20     25     30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35     40     45
Asp Thr Arg Tyr Gln Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50     55     60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65     70     75     80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
85     90     95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
100    105    110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115    120    125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130    135    140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145    150    155    160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165    170    175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180    185    190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195    200    205
Asn Arg Gly Glu Cys
210

```

<210> 230

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VH Chain

<400> 230

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1      5      10      15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20     25     30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35     40     45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
50     55     60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65     70     75     80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
85     90     95
Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Gln
100    105    110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115    120    125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130    135    140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145    150    155    160

```

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

&lt;210&gt; 231

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 231

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro

```

          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
          115          120          125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
          130          135          140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
          165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
          180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
          195          200          205
Asn Arg Gly Glu Cys
          210

```

&lt;210&gt; 232

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 232

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1          5          10          15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20          25          30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35          40          45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
          50          55          60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
          65          70          75          80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85          90          95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
          100          105          110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
          115          120          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
          130          135          140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
          145          150          155          160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
          165          170          175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
          180          185          190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
          195          200          205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
          210          215          220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
          225          230          235          240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
          245          250          255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
          260          265          270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
          275          280          285

```

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450  
 <210> 233  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> Humanized antibody - VL Chain

<400> 233

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 234

<211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 234  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His

<400> 236  
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
1 5 10 15  
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
20 25 30  
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
35 40 45  
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser

50		55		60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val				
65		70		75
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr				80
	85		90	
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln				95
	100		105	
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val				110
	115		120	
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala				125
	130		135	
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser				140
145		150		155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val				160
	165		170	
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro				175
	180		185	
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys				190
	195		200	
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp				205
	210		215	
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly				220
225		230		235
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile				240
	245		250	
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu				255
	260		265	
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His				270
	275		280	
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg				285
	290		295	
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys				300
305		310		315
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu				320
	325		330	
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr				335
	340		345	
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu				350
	355		360	
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp				365
	370		375	
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val				380
385		390		395
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp				400
	405		410	
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His				415
	420		425	
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro				430
	435		440	
Gly Lys			445	
450				

&lt;210&gt; 237

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 237

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile Tyr
      35      40      45
Asp Thr Arg Tyr Leu Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
      65      70      75      80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
      100      105      110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
      115      120      125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130      135      140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
      145      150      155      160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165      170      175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180      185      190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195      200      205
Asn Arg Gly Glu Cys
      210

```

&lt;210&gt; 238

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 238

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1      5      10      15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20      25      30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35      40      45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
      50      55      60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
      65      70      75      80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85      90      95
Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln
      100      105      110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115      120      125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130      135      140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
      145      150      155      160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165      170      175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro

```



```

      180      185      190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195      200      205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
      210      215      220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225      230      235      240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
      245      250      255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
      260      265      270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
      275      280      285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290      295      300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305      310      315      320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
      325      330      335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
      340      345      350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
      355      360      365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
      370      375      380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385      390      395      400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
      405      410      415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
      420      425      430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
      435      440      445
Gly Lys
      450

```

&lt;210&gt; 239

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 239

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile Tyr
      35      40      45
Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65      70      75      80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
100      105      110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115      120      125

```

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 240  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 240  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Ser Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys

```

305              310              315              320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
              325              330              335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
              340              345              350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
              355              360              365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
              370              375              380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385              390              395              400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
              405              410              415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
              420              425              430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
              435              440              445
Gly Lys
450

```

```

<210> 241
<211> 213
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VH Chain

```

```

<400> 241
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1              5              10              15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
              20              25              30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
              35              40              45
Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50              55              60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65              70              75              80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Phe Tyr Pro Phe Thr
              85              90              95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
              100              105              110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
              115              120              125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130              135              140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145              150              155              160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
              165              170              175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
              180              185              190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195              200              205
Asn Arg Gly Glu Cys
210

```

```

<210> 242
<211> 450
<212> PRT

```

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 242

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1      5      10      15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
20      25      30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35      40      45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
50      55      60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65      70      75      80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
85      90      95
Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln
100     105     110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115     120     125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130     135     140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145     150     155     160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165     170     175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180     185     190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195     200     205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210     215     220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225     230     235     240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245     250     255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260     265     270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275     280     285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290     295     300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305     310     315     320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325     330     335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340     345     350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355     360     365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370     375     380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385     390     395     400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405     410     415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420     425     430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro

```

435                                      440                                      445  
 Gly Lys  
 450  
  
 <210> 243  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence  
  
 <220>  
 <223> Humanized antibody - VL Chain  
  
 <400> 243  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1                                      5                                      10                                      15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
                                     20                                      25                                      30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
                                     35                                      40                                      45  
 Asp Thr Phe Lys Leu Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
                                     50                                      55                                      60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65                                      70                                      75                                      80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
                                     85                                      90                                      95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
                                     100                                      105                                      110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
                                     115                                      120                                      125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
                                     130                                      135                                      140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145                                      150                                      155                                      160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
                                     165                                      170                                      175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
                                     180                                      185                                      190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
                                     195                                      200                                      205  
 Asn Arg Gly Glu Cys  
 210  
  
 <210> 244  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence  
  
 <220>  
 <223> Humanized antibody - VH Chain  
  
 <400> 244  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1                                      5                                      10                                      15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
                                     20                                      25                                      30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
                                     35                                      40                                      45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
                                     50                                      55                                      60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65                                      70                                      75                                      80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
                             85                            90                            95  
 Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln  
                             100                            105                            110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
                             115                            120                            125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
                             130                            135                            140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145                            150                            155                            160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
                             165                            170                            175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
                             180                            185                            190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
                             195                            200                            205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
                             210                            215                            220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225                            230                            235                            240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
                             245                            250                            255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
                             260                            265                            270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
                             275                            280                            285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
                             290                            295                            300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305                            310                            315                            320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
                             325                            330                            335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
                             340                            345                            350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
                             355                            360                            365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
                             370                            375                            380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385                            390                            395                            400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
                             405                            410                            415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
                             420                            425                            430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
                             435                            440                            445  
 Gly Lys  
                             450

&lt;210&gt; 245

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 245

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1                            5                            10                            15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met

```

                20                25                30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35                40                45
Asp Thr Phe Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50                55                60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70                75                80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85                90                95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
           100                105                110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
           115                120                125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
           130                135                140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145           150                155                160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
           165                170                175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
           180                185                190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
           195                200                205
Asn Arg Gly Glu Cys
           210

```

<210> 246  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

```

<400> 246
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
           20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
           35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
           50           55           60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
           85           90           95
Cys Ala Arg Asp Met Ile Thr Asn Phe Tyr Phe Asp Val Trp Gly Gln
           100          105          110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
           115          120          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
           130          135          140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145           150          155          160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
           165          170          175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
           180          185          190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
           195          200          205

```

```

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
  210                215                220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                230                235                240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                250                255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
                260                265                270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                275                280                285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                290                295                300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                310                315                320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                330                335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                340                345                350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                355                360                365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                370                375                380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                390                395                400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                410                415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
                420                425                430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                435                440                445
Gly Lys
  450

```

<210> 247  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Chain

```

<400> 247
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1                5                10                15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
                20                25                30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                35                40                45
Asp Thr Phe Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                50                55                60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                70                75                80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                90                95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
                100                105                110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
                115                120                125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130                135                140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu

```



```

145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
          165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
          180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
          195          200          205
Asn Arg Gly Glu Cys
          210

```

```

<210> 248
<211> 450
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VH Chain

```

```

<400> 248
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1      5      10      15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20      25      30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35      40      45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser
50      55      60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65      70      75      80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85      90      95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
          100     105     110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
          115     120     125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130     135     140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145     150     155     160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
          165     170     175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
          180     185     190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195     200     205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210     215     220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225     230     235     240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
          245     250     255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260     265     270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275     280     285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290     295     300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305     310     315     320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
          325     330     335

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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
                   340                  345                  350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
                   355                  360                  365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
                   370                  375                  380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
                   385                  390                  395                  400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
                   405                  410                  415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
                   420                  425                  430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
                   435                  440                  445  
 Gly Lys  
                   450

&lt;210&gt; 249

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 249

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1                  5                  10                  15  
 Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Arg Val Gly Tyr Met  
                   20                  25                  30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
                   35                  40                  45  
 Asp Thr Tyr Arg His Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
                   50                  55                  60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
                   65                  70                  75                  80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
                   85                  90                  95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
                   100                  105                  110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
                   115                  120                  125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
                   130                  135                  140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
                   145                  150                  155                  160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
                   165                  170                  175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
                   180                  185                  190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
                   195                  200                  205  
 Asn Arg Gly Glu Cys  
                   210

&lt;210&gt; 250

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 250

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1          5          10          15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
20          25          30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35          40          45
Trp Leu Ala Asp Ile Trp Trp Asp Gly Lys Lys His Tyr Asn Pro Ser
50          55          60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65          70          75          80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
85          90          95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
100         105         110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115         120         125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130         135         140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145         150         155         160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165         170         175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180         185         190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195         200         205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210         215         220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225         230         235         240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245         250         255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260         265         270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275         280         285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290         295         300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305         310         315         320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325         330         335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340         345         350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355         360         365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370         375         380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385         390         395         400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405         410         415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420         425         430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435         440         445
Gly Lys
450

```

<210> 251  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Chain

<400> 251  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Phe His Arg Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 252  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 252  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

&lt;210&gt; 253

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 253

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Leu Leu Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser

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      50              55              60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65              70              75              80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85              90              95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
      100              105              110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
      115              120              125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130              135              140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145              150              155              160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165              170              175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180              185              190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195              200              205
Asn Arg Gly Glu Cys
      210

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&lt;210&gt; 254

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 254

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1              5              10              15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20              25              30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35              40              45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser
      50              55              60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65              70              75              80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85              90              95
Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
      100              105              110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115              120              125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130              135              140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145              150              155              160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165              170              175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180              185              190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195              200              205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
      210              215              220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225              230              235              240

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[illegible]

<210> 255

$\langle 211 \rangle$       213

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$ 

<223> Humanized antibody - VL Chain

<400> 255

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Ser	Ala	Ser	Ser	Arg	Val	Gly	Tyr	Met
			20					25					30		
His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr
			35				40					45			
Asp	Thr	Ser	Lys	Leu	Ala	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser
						55					60				
Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Asp
65					70					75					80
Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Phe	Gln	Gly	Ser	Gly	Tyr	Pro	Phe	Thr
				85					90					95	
Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	Pro
				100				105					110		
Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr
							120					125			
Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys
						135					140				
Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu
145					150					155					160
Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser
				165					170					175	
Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala

180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 256  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 256  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365



Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

<210> 257  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Chain

<400> 257  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Ser Phe Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro  
 100 105 110  
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr  
 115 120 125  
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 258  
 <211> 26  
 <212> DNA  
 <213> Artificial

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 258  
 agtgtcttaa ccagcaaagt gttaga

<210> 259  
 <211> 26  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 259  
 tcattgactt gagatattga tgcac 26

<210> 260  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 260  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
 1 5 10 15

<210> 261  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 261  
 Glu Ser Gly Arg Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
 1 5 10 15

<210> 262  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 262  
 Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr  
 1 5 10

<210> 263  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 263  
 Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gln  
 1 5 10 15

<210> 264

<211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 264  
 Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Val Asp  
 1 5 10

<210> 265  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 265  
 Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Lys Gly  
 1 5 10

<210> 266  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 266  
 Lys Glu Ser Gly Ser Val Ser Ser Glu Gln Leu Ala Gln Phe Arg Ser  
 1 5 10 15

Leu Asp

<210> 267  
 <211> 16  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Linker for constructing humanized antibodies

<400> 267  
 Glu Ser Gly Ser Val Ser Ser Glu Glu Leu Ala Phe Arg Ser Leu Asp  
 1 5 10 15

<210> 268  
 <211> 4  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> intrabody

<400> 268  
 Lys Asp Glu Leu  
 1

<210> 269  
<211> 4  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 269  
Asp Asp Glu Leu  
1

<210> 270  
<211> 4  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 270  
Asp Glu Glu Leu  
1

<210> 271  
<211> 4  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 271  
Gln Glu Asp Leu  
1

<210> 272  
<211> 4  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 272  
Arg Asp Glu Leu  
1

<210> 273  
<211> 7  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 273  
Pro Lys Lys Lys Arg Lys Val  
1 5

<210> 274  
<211> 7  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 274  
Pro Gln Lys Lys Ile Lys Ser  
1 5

<210> 275  
<211> 5  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 275  
Gln Pro Lys Lys Pro  
1 5

<210> 276  
<211> 4  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 276  
Arg Lys Lys Arg  
1

<210> 277  
<211> 5  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 277  
Lys Lys Lys Arg Lys  
1 5

<210> 278  
<211> 12  
<212> PRT  
<213> Homo sapiens

<220>  
<223> intrabody

<400> 278  
Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala His Gln  
1 5 10

<210> 279

<211> 16  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> intrabody

<400> 279  
 Arg Gln Ala Arg Arg Asn Arg Arg Arg Arg Trp Arg Glu Arg Gln Arg  
 1 5 10 15

<210> 280  
 <211> 19  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> intrabody

<400> 280  
 Met Pro Leu Thr Arg Arg Arg Pro Ala Ala Ser Gln Ala Leu Ala Pro  
 1 5 10 15

Pro Thr Pro

<210> 281  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> intrabody

<400> 281  
 Met Asp Asp Gln Arg Asp Leu Ile Ser Asn Asn Glu Gln Leu Pro  
 1 5 10 15

<210> 282  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> intrabody

<220>  
 <221> misc\_feature  
 <222> 7, 8, 32,  
 <223> Xaa can be any naturally occurring amino acid

<400> 282  
 Met Leu Phe Asn Leu Arg Xaa Xaa Leu Asn Asn Ala Ala Phe Arg His  
 1 5 10 15

Gly His Asn Phe Met Val Arg Asn Phe Arg Cys Gly Gln Pro Leu Xaa  
 20 25 30

<210> 283  
 <211> 3  
 <212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 283

Ala Lys Leu

1

<210> 284

<211> 6

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 284

Ser Asp Tyr Gln Arg Leu

1

5

<210> 285

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 285

Gly Cys Val Cys Ser Ser Asn Pro

1

5

<210> 286

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 286

Gly Gln Thr Val Thr Thr Pro Leu

1

5

<210> 287

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 287

Gly Gln Glu Leu Ser Gln His Glu

1

5

<210> 288

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 288

Gly Asn Ser Pro Ser Tyr Asn Pro

1 5

<210> 289

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 289

Gly Val Ser Gly Ser Lys Gly Gln

1 5

<210> 290

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 290

Gly Gln Thr Ile Thr Thr Pro Leu

1 5

<210> 291

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 291

Gly Gln Thr Leu Thr Thr Pro Leu

1 5

<210> 292

<211> 8

<212> PRT

<213> Homo sapiens

<220>

<223> intrabody

<400> 292

Gly Gln Ile Phe Ser Arg Ser Ala

1 5

<210> 293

<211> 8

<212> PRT

<213> Homo sapiens



&lt;220&gt;

&lt;223&gt; intrabody

&lt;400&gt; 293

Gly Gln Ile His Gly Leu Ser Pro  
1 5

&lt;210&gt; 294

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; intrabody

&lt;400&gt; 294

Gly Ala Arg Ala Ser Val Leu Ser  
1 5

&lt;210&gt; 295

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; intrabody

&lt;400&gt; 295

Gly Cys Thr Leu Ser Ala Glu Glu  
1 5

&lt;210&gt; 296

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; intrabody

&lt;400&gt; 296

Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro  
1 5 10 15

&lt;210&gt; 297

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; intrabody

&lt;400&gt; 297

Ala Ala Val Leu Leu Pro Val Leu Leu Ala Ala Pro  
1 5 10

&lt;210&gt; 298

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; intrabody

&lt;400&gt; 298

Val Thr Val Leu Ala Leu Gly Ala Leu Ala Gly Val Gly Val Gly  
 1 5 10 15

&lt;210&gt; 299

&lt;211&gt; 30

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 299

ccagcagtac cacttccttg ccctgcgccg 30

&lt;210&gt; 300

&lt;211&gt; 30

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 300

gccgcgtccc gttccttcac catgacgacc 30

&lt;210&gt; 301

&lt;211&gt; 31

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 301

ccagcagtac cgcttccttg ccctgcggcc g 31

&lt;210&gt; 302

&lt;211&gt; 30

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 302

gccgcgtccc gttccttcac catgacgacc 30

&lt;210&gt; 303

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 303

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln

```

1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35           40           45
Trp Leu Ala Asp Ile Trp Trp Gly Asp Lys Gly His Tyr Asn Pro Ser
      50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
      65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85           90           95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
      100           105           110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115           120           125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130           135           140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
      145           150           155           160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165           170           175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180           185           190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195           200           205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
      210           215           220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
      225           230           235           240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
      245           250           255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
      260           265           270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
      275           280           285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
      290           295           300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
      305           310           315           320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
      325           330           335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
      340           345           350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
      355           360           365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
      370           375           380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
      385           390           395           400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
      405           410           415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
      420           425           430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
      435           440           445
Gly Lys
      450

```

&lt;210&gt; 304

&lt;211&gt; 120

&lt;212&gt; PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VH Domain

<400> 304

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1          5          10          15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20          25          30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35          40          45
Trp Leu Ala Asp Ile Trp Trp Gly Asp Lys Gly His Tyr Asn Pro Ser
          50          55          60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65          70          75          80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85          90          95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
          100          105          110
Gly Thr Thr Val Thr Val Ser Ser
          115          120

```

<210> 305

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 305

```

Asp Ile Trp Trp Gly Asp Lys Gly His Tyr Asn Pro Ser Leu Lys Asp
1          5          10          15

```

<210> 306

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VL Chain

<400> 306

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1          5          10          15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met
          20          25          30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35          40          45
Asp Thr Phe Tyr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50          55          60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65          70          75          80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85          90          95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
          115          120          125

```

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys  
 130 135 140  
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu  
 145 150 155 160  
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser  
 165 170 175  
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala  
 180 185 190  
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe  
 195 200 205  
 Asn Arg Gly Glu Cys  
 210

<210> 307  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

<400> 307  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Tyr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95  
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> 308  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

<400> 308  
 Asp Thr Phe Tyr Leu His Ser  
 1 5

<210> 309  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 309  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln

```

1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser
50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
85           90           95
Cys Ala Arg Asp Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Gln
100          105          110
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115          120          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130          135          140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145          150          155          160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165          170          175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180          185          190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195          200          205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210          215          220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225          230          235          240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245          250          255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260          265          270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275          280          285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290          295          300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305          310          315          320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325          330          335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340          345          350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355          360          365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370          375          380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385          390          395          400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405          410          415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420          425          430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435          440          445
Gly Lys
450

```

&lt;210&gt; 310

&lt;211&gt; 120

&lt;212&gt; PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VH Domain

<400> 310

```

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
          20           25           30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35           40           45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Ser Tyr Asn Pro Ser
          50           55           60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
          85           90           95
Cys Ala Arg Asp Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Gln
          100          105          110
Gly Thr Thr Val Thr Val Ser Ser
          115          120

```

<210> 311

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 311

```

Asp Met Ile Thr Asn Trp Tyr Phe Asp Val
1           5           10

```

<210> 312

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized antibody - VL Chain

<400> 312

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Leu Leu Ser Ser Arg Val Gly Tyr Met
          20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35           40           45
Asp Thr Tyr Tyr Gln Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr

```

```

      115              120              125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130              135              140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145              150              155              160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165              170              175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180              185              190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195              200              205
Asn Arg Gly Glu Cys
      210

```

<210> 313  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

```

<400> 313
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Leu Leu Ser Ser Arg Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35      40      45
Asp Thr Tyr Tyr Gln Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65      70      75      80
Asp Phe Ala Thr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 314  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

```

<400> 314
Leu Leu Ser Ser Arg Val Gly Tyr Met His
1      5      10

```

<210> 315  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions



<400> 315  
 Asp Thr Tyr Tyr Gln Thr Ser  
 1 5

<210> 316  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

<400> 316  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

```

      370              375              380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385              390              395              400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
      405              410              415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
      420              425              430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
      435              440              445
Gly Lys
      450

```

```

<210> 317
<211> 120
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VH Domain

```

```

<400> 317
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1              5              10              15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
      20              25              30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35              40              45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser
      50              55              60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
      65              70              75              80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
      85              90              95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
      100              105              110
Gly Thr Thr Val Thr Val Ser Ser
      115              120

```

```

<210> 318
<211> 213
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VL Chain

```

```

<400> 318
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1              5              10              15
Asp Arg Val Thr Ile Thr Cys Leu Leu Ser Ser Arg Val Gly Tyr Met
      20              25              30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35              40              45
Asp Thr Met Tyr Gln Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50              55              60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
      65              70              75              80
Asp Phe Ala Thr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85              90              95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
      100              105              110

```

```

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
      115                      120                      125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130                      135                      140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                      150                      155                      160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165                      170                      175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180                      185                      190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195                      200                      205
Asn Arg Gly Glu Cys
      210

```

<210> 319  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

```

<400> 319
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Leu Leu Ser Ser Arg Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35      40      45
Asp Thr Met Tyr Gln Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
      65      70      75      80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 320  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

```

<400> 320
Leu Leu Ser Ser Arg Val Gly Tyr Met His
1      5      10

```

<210> 321  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid

## substitutions

&lt;400&gt; 321

Asp Thr Met Tyr Gln Ala Ser

1

5

&lt;210&gt; 322

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VH Chain

&lt;400&gt; 322

Gln	Val	Thr	Leu	Arg	Glu	Ser	Gly	Pro	Ala	Leu	Val	Lys	Pro	Thr	Gln
1				5					10					15	
Thr	Leu	Thr	Leu	Thr	Cys	Thr	Phe	Ser	Gly	Phe	Ser	Leu	Ser	Thr	Ala
			20					25					30		
Gly	Met	Ser	Val	Gly	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Ala	Leu	Glu
		35					40					45			
Trp	Leu	Ala	Asp	Ile	Trp	Trp	Asp	Asp	Lys	Lys	His	Tyr	Asn	Pro	Ser
	50					55					60				
Leu	Lys	Asp	Arg	Leu	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Lys	Asn	Gln	Val
65					70					75				80	
Val	Leu	Lys	Val	Thr	Asn	Met	Asp	Pro	Ala	Asp	Thr	Ala	Thr	Tyr	Tyr
				85					90					95	
Cys	Ala	Arg	Asp	Met	Ile	Phe	Asn	Trp	Tyr	Phe	Asp	Val	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
		115					120					125			
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
	130						135				140				
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
145					150					155					160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
			165						170					175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
		180						185					190		
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
	195						200					205			
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
	210					215					220				
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
225					230					235					240
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
			245						250					255	
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
		260						265					270		
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		275					280					285			
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
	290					295					300				
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
305					310					315					320
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
				325					330					335	
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
		340						345					350		
Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
		355					360						365		

```

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370                               375                               380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                               390                               395                               400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                               405                               410                               415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
                               420                               425                               430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                               435                               440                               445
Gly Lys
 450

```

```

<210> 323
<211> 120
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VH Domain

```

```

<400> 323
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1                               5                               10                               15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
                               20                               25                               30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
                               35                               40                               45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser
                               50                               55                               60
Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                               70                               75                               80
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
                               85                               90                               95
Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln
                               100                              105                              110
Gly Thr Thr Val Thr Val Ser Ser
                               115                              120

```

```

<210> 324
<211> 213
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VL Chain

```

```

<400> 324
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1                               5                               10                               15
Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met
                               20                               25                               30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                               35                               40                               45
Asp Thr Tyr Tyr Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                               50                               55                               60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                               70                               75                               80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                               85                               90                               95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro

```

```

          100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
          115          120          125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
          130          135          140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
          165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
          180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
          195          200          205
Asn Arg Gly Glu Cys
          210

```

<210> 325  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Domain

```

<400> 325
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met
          20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
          35      40      45
Asp Thr Tyr Tyr Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
          50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
          65      70      75      80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
          85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100      105

```

<210> 326  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

```

<400> 326
Asp Thr Tyr Tyr Leu Pro Ser
1      5

```

<210> 327  
 <211> 450  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Chain

&lt;400&gt; 327

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val  
 115 120 125  
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
 130 135 140  
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser  
 145 150 155 160  
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val  
 165 170 175  
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro  
 180 185 190  
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys  
 195 200 205  
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp  
 210 215 220  
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly  
 225 230 235 240  
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile  
 245 250 255  
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu  
 260 265 270  
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
 275 280 285  
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg  
 290 295 300  
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys  
 305 310 315 320  
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu  
 325 330 335  
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
 340 345 350  
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu  
 355 360 365  
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp  
 370 375 380  
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val  
 385 390 395 400  
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp  
 405 410 415  
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His  
 420 425 430  
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro  
 435 440 445  
 Gly Lys  
 450

<210> 328  
 <211> 120  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VH Domain

<400> 328  
 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala  
 20 25 30  
 Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val  
 65 70 75 80  
 Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Met Ile Phe Asn Trp Tyr Phe Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> 329  
 <211> 16  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Amino acid sequence derived from Murine monoclonal  
 antibody and further modified by amino acid  
 substitutions

<400> 329  
 Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser Leu Lys Asp  
 1 5 10 15

<210> 330  
 <211> 213  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Humanized antibody - VL Chain

<400> 330  
 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met  
 20 25 30  
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
 35 40 45  
 Asp Thr Phe Arg His Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
 50 55 60  
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp  
 65 70 75 80  
 Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr  
 85 90 95



```

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
      100                      105                      110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
      115                      120                      125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
      130                      135                      140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
      145                      150                      155                      160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
      165                      170                      175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
      180                      185                      190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
      195                      200                      205

```

```

Asn Arg Gly Glu Cys
      210

```

```

<210> 331
<211> 106
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Humanized antibody - VL Domain

```

```

<400> 331
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Leu Ser Ser Arg Val Gly Tyr Met
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
      35      40      45
Asp Thr Phe Arg His Thr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
      50      55      60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
      65      70      75      80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
      85      90      95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100      105

```

```

<210> 332
<211> 7
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Amino acid sequence derived from Murine monoclonal
antibody and further modified by amino acid
substitutions

```

```

<400> 332
Asp Thr Phe Arg His Thr Ser
1      5

```

```

<210> 333
<211> 213
<212> PRT
<213> Artificial Sequence

```

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Chain

&lt;400&gt; 333

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Ser Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Tyr Tyr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
           100          105          110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
           115          120          125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
           130          135          140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145          150          155          160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
           165          170          175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
           180          185          190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
           195          200          205
Asn Arg Gly Glu Cys
           210

```

&lt;210&gt; 334

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Humanized antibody - VL Domain

&lt;400&gt; 334

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Ser Pro Ser Ser Ser Val Gly Tyr Met
           20           25           30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
           35           40           45
Asp Thr Tyr Tyr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
           50           55           60
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65           70           75           80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
           85           90           95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
           100          105

```

&lt;210&gt; 335

&lt;211&gt; 10

&lt;212&gt; PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 335

Ser Pro Ser Ser Ser Val Gly Tyr Met His  
1 5 10

<210> 336

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 336

Asp Thr Tyr Tyr Leu Ala Ser  
1 5

<210> 337

<211> 365

<212> FRT

<213> Homo sapiens

<220>

<223> Human FcRn

<400> 337

Met Gly Val Pro Arg Pro Gln Pro Trp Ala Leu Gly Leu Leu Leu Phe  
1 5 10 15  
Leu Leu Pro Gly Ser Leu Gly Ala Glu Ser His Leu Ser Leu Leu Tyr  
20 25 30  
His Leu Thr Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp  
35 40 45  
Val Ser Gly Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu  
50 55 60  
Arg Gly Glu Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val  
65 70 75 80  
Ser Trp Tyr Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys  
85 90 95  
Leu Phe Leu Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr  
100 105 110  
Leu Gln Gly Leu Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val  
115 120 125  
Pro Thr Ala Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp  
130 135 140  
Leu Lys Gln Gly Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile  
145 150 155 160  
Ser Gln Arg Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr  
165 170 175  
Phe Leu Leu Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg  
180 185 190  
Gly Arg Gly Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys  
195 200 205  
Ala Arg Pro Ser Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe

```

      210              215              220
Ser Phe Tyr Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu
225              230              235              240
Ala Ala Gly Thr Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser
      245              250              255
Phe His Ala Ser Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His
      260              265              270
Tyr Cys Cys Ile Val Gln His Ala Gly Leu Ala Gln Pro Leu Arg Val
      275              280              285
Glu Leu Glu Ser Pro Ala Lys Ser Ser Val Leu Val Val Gly Ile Val
      290              295              300
Ile Gly Val Leu Leu Leu Thr Ala Ala Ala Val Gly Gly Ala Leu Leu
305              310              315              320
Trp Arg Arg Met Arg Ser Gly Leu Pro Ala Pro Trp Ile Ser Leu Arg
      325              330              335
Gly Asp Asp Thr Gly Val Leu Leu Pro Thr Pro Gly Glu Ala Gln Asp
      340              345              350
Ala Asp Leu Lys Asp Val Asn Val Ile Pro Ala Thr Ala
      355              360              365

```

<210> 338  
 <211> 365  
 <212> PRT  
 <213> Murine

```

<400> 338
Met Gly Met Pro Leu Pro Trp Ala Leu Ser Leu Leu Leu Val Leu Leu
1      5      10      15
Pro Gln Thr Trp Gly Ser Glu Thr Arg Pro Pro Leu Met Tyr His Leu
      20      25      30
Thr Ala Val Ser Asn Pro Ser Thr Gly Leu Pro Ser Phe Trp Ala Thr
      35      40      45
Gly Trp Leu Gly Pro Gln Gln Tyr Leu Thr Tyr Asn Ser Leu Arg Gln
      50      55      60
Glu Ala Asp Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp
      65      70      75      80
Tyr Trp Glu Lys Glu Thr Thr Asp Leu Lys Ser Lys Glu Gln Leu Phe
      85      90      95
Leu Glu Ala Leu Lys Thr Leu Glu Lys Ile Leu Asn Gly Thr Tyr Thr
      100     105     110
Leu Gln Gly Leu Leu Gly Cys Glu Leu Ala Ser Asp Asn Ser Ser Val
      115     120     125
Pro Thr Ala Val Phe Ala Leu Asn Gly Glu Glu Phe Met Lys Phe Asn
      130     135     140
Pro Arg Ile Gly Asn Trp Thr Gly Glu Trp Pro Glu Thr Glu Ile Val
      145     150     155     160
Ala Asn Leu Trp Met Lys Gln Pro Asp Ala Ala Arg Lys Glu Ser Glu
      165     170     175
Phe Leu Leu Asn Ser Cys Pro Glu Arg Leu Leu Gly His Leu Glu Arg
      180     185     190
Gly Arg Arg Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys
      195     200     205
Ala Arg Pro Gly Asn Ser Gly Ser Ser Val Leu Thr Cys Ala Ala Phe
      210     215     220
Ser Phe Tyr Pro Pro Glu Leu Lys Phe Arg Phe Leu Arg Asn Gly Leu
      225     230     235     240
Ala Ser Gly Ser Gly Asn Cys Ser Thr Gly Pro Asn Gly Asp Gly Ser
      245     250     255
Phe His Ala Trp Ser Leu Leu Glu Val Lys Arg Gly Asp Glu His His
      260     265     270
Tyr Gln Cys Gln Val Glu His Glu Gly Leu Ala Gln Pro Leu Thr Val

```

```

      275              280              285
Asp Leu Asp Ser Ser Ala Arg Ser Ser Val Pro Val Val Gly Ile Val
      290              295              300
Leu Gly Leu Leu Leu Val Val Val Ala Ile Ala Gly Gly Val Leu Leu
305              310              315              320
Trp Gly Arg Met Arg Ser Gly Leu Pro Ala Pro Trp Leu Ser Leu Ser
      325              330              335
Gly Asp Asp Ser Gly Asp Leu Leu Pro Gly Gly Asn Leu Pro Pro Glu
      340              345              350
Ala Glu Pro Gln Gly Ala Asn Ala Phe Pro Ala Thr Ser
      355              360              365

```

```

<210> 339
<211> 110
<212> PRT
<213> Homo sapiens

```

```

<400> 339
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1              5              10              15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
      20              25              30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
      35              40              45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50              55              60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65              70              75              80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
      85              90              95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
      100              105              110

```

```

<210> 340
<211> 107
<212> PRT
<213> Homo sapiens

```

```

<400> 340
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
1              5              10              15
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
      20              25              30
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
      35              40              45
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50              55              60
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65              70              75              80
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
      85              90              95
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      100              105

```

```

<210> 341
<211> 15
<212> PRT
<213> Homo sapiens

```

```

<400> 341
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro

```

1	5	10	15
<210>	342		
<211>	232		
<212>	PRT		
<213>	Homo sapiens		
<220>			
<223>	Human hinge Fc region		
<400>	342		
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala			
1 5 10 15			
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro			
20 25 30			
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val			
35 40 45			
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val			
50 55 60			
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln			
65 70 75 80			
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln			
85 90 95			
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala			
100 105 110			
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro			
115 120 125			
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr			
130 135 140			
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser			
145 150 155 160			
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr			
165 170 175			
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr			
180 185 190			
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe			
195 200 205			
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys			
210 215 220			
Ser Leu Ser Leu Ser Pro Gly Lys			
225 230			
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20 25 30			
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu			
35 40 45			
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser			
50 55 60			
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val			
65 70 75 80			

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr  
                   85                  90                  95  
 Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Gln  
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 Gly Thr Thr Val Thr Val Ser Ser  
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Gly Gln Pro Glu Asn  
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<400> 368

His Arg Ser Glu Asn

1 5

<210> 369

<211> 5

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1 5

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<211> 5

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Gly Ile Thr Glu Ser

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<211> 5

<212> PRT

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Ser Met Ala Glu Pro

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1 5

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<210> 378

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<210> 379  
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 TAAssDNA template to make Library 2

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<210> 380  
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<210> 381  
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<210> 383

<211> 45

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antibody and further modified by amino acid  
substitutions

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<210> 385

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antibody and further modified by amino acid  
substitutions

<400> 385

Asp	Ile	Trp	Trp	Asp	Asp	Lys	Gly	Asp	Tyr	Asn	Pro	Ser	Leu	Lys	Asp
1				5				10						15	

<210> 386

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antibody and further modified by amino acid  
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<210> 387  
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1 5 10 15

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antibody and further modified by amino acid  
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<400> 391

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<210> 392

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<400> 392

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<210> 393

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<400> 393

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<210> 394

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<400> 394

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<210> 395

<211> 16

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antibody and further modified by amino acid  
substitutions

<400> 395

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1 5 10 15

<210> 396

<211> 10

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antibody and further modified by amino acid  
substitutions

<400> 396

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antibody and further modified by amino acid  
substitutions

<400> 397

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antibody and further modified by amino acid  
substitutions

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<211> 10

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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

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substitutions

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antibody and further modified by amino acid  
substitutions

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<210> 419

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antibody and further modified by amino acid  
substitutions

<400> 419

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<210> 420

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antibody and further modified by amino acid  
substitutions

<400> 420

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1 5 10

<210> 421  
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<210> 422  
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<210> 424  
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<210> 425  
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<212> PRT  
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substitutions

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substitutions

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antibody and further modified by amino acid  
substitutions

<400> 429

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<210> 430

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antibody and further modified by amino acid  
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&lt;400&gt; 560

Asp Thr Ser Gly His His Ser

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&lt;210&gt; 561

&lt;211&gt; 7

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&lt;400&gt; 561

Asp Thr Ser Gly His Pro Ser

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&lt;210&gt; 562

&lt;211&gt; 7

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&lt;213&gt; Artificial Sequence

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&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 562

Asp Thr Ser Gly His Thr Ser

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&lt;210&gt; 563

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 563

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&lt;210&gt; 564

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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&lt;210&gt; 574

&lt;211&gt; 7

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antibody and further modified by amino acid

substitutions

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&lt;210&gt; 575

&lt;211&gt; 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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&lt;400&gt; 586

Asp Thr Ser Arg His Asp Ser

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&lt;210&gt; 587

&lt;211&gt; 7

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&lt;213&gt; Artificial Sequence

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&lt;400&gt; 587

Asp Thr Ser Arg Gln Ala Ser

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&lt;210&gt; 588

&lt;211&gt; 7

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&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 588

Asp Thr Ser Arg Gln Ser Ser

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&lt;210&gt; 589

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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&lt;210&gt; 590

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
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substitutions

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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&lt;210&gt; 682

&lt;211&gt; 7

&lt;212&gt; PRT

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antibody and further modified by amino acid  
substitutions

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&lt;210&gt; 683

&lt;211&gt; 7

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&lt;400&gt; 683

Asp Thr Phe Gly Leu Ser Ser  
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&lt;210&gt; 684

&lt;211&gt; 7

&lt;212&gt; PRT

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 684

Asp Thr Phe Gly Leu Lys Ser  
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&lt;210&gt; 685

&lt;211&gt; 7

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
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&lt;400&gt; 685

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antibody and further modified by amino acid  
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<210> 696

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substitutions

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&lt;210&gt; 708

&lt;211&gt; 7

&lt;212&gt; PRT

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&lt;210&gt; 709

&lt;211&gt; 7

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&lt;210&gt; 710

&lt;211&gt; 7

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<223> Amino acid sequence derived from Murine monoclonal  
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substitutions

&lt;400&gt; 710

Asp Thr Phe Arg Leu His Ser  
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&lt;210&gt; 711

&lt;211&gt; 7

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&lt;213&gt; Artificial Sequence

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<210> 718

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<210> 861

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<210> 862

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<210> 863

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<210> 864

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&lt;400&gt; 913

Asp Thr Tyr Phe Gln Lys Ser

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&lt;210&gt; 914

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;400&gt; 914

Asp Thr Tyr Phe Gln Arg Ser

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&lt;210&gt; 915

&lt;211&gt; 7

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&lt;400&gt; 915

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&lt;210&gt; 916

&lt;211&gt; 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<210> 944

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<210> 947

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antibody and further modified by amino acid  
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<210> 950

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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Asp Thr Arg Gly His Ala Ser  
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<210> 969

<211> 7

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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Asp Thr Arg Gly His Ser Ser  
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<210> 970

<211> 7

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Asp Thr Arg Gly His Lys Ser  
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<210> 971

<211> 7

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Asp Thr Arg Gly His Arg Ser  
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<210> 972

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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Asp Thr Arg Gly His Thr Ser  
1 5

<210> 975  
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antibody and further modified by amino acid  
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1 5

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antibody and further modified by amino acid  
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<210> 977

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<210> 978

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<210> 979

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<210> 980

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<210> 981

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<210> 982

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<210> 983

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<210> 984

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<210> 985

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Asp Thr Arg Arg Leu Ser Ser  
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<210> 986

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<210> 989

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

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<210> 995

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antibody and further modified by amino acid  
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1 5

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antibody and further modified by amino acid  
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<210> 997

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antibody and further modified by amino acid  
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<210> 998

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antibody and further modified by amino acid  
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&lt;210&gt; 999

&lt;211&gt; 7

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&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 999

Asp Thr Arg Arg His Asp Ser

1

5

&lt;210&gt; 1000

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1000

Asp Thr Arg Arg Gln Ala Ser

1

5

&lt;210&gt; 1001

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1001

Asp Thr Arg Arg Gln Ser Ser

1

5

&lt;210&gt; 1002

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1002

Asp Thr Arg Arg Gln Lys Ser

1

5

&lt;210&gt; 1003

&lt;211&gt; 7

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<210> 1004

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antibody and further modified by amino acid  
substitutions

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<210> 1008

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antibody and further modified by amino acid  
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<400> 1008

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<210> 1009

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antibody and further modified by amino acid  
substitutions

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1 5

<210> 1010

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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

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<211> 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<211> 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<210> 1048

<211> 7

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antibody and further modified by amino acid  
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<210> 1049

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antibody and further modified by amino acid  
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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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Asp Thr Arg Leu Leu Ala Ser  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
substitutions

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<210> 1062

<211> 7

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antibody and further modified by amino acid  
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<210> 1063

<211> 7

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antibody and further modified by amino acid
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<210> 1076

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antibody and further modified by amino acid  
substitutions

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&lt;400&gt; 1077

Asp Thr Met Lys Leu Arg Ser

1

5

&lt;210&gt; 1078

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1078

Asp Thr Met Lys Leu His Ser

1

5

&lt;210&gt; 1079

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1079

Asp Thr Met Lys Leu Pro Ser

1

5

&lt;210&gt; 1080

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1080

Asp Thr Met Lys Leu Thr Ser

1

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&lt;210&gt; 1081

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<210> 1082

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<210> 1087

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antibody and further modified by amino acid  
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<210> 1088

<211> 7

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antibody and further modified by amino acid  
substitutions

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<210> 1089

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antibody and further modified by amino acid  
substitutions

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1

5

&lt;210&gt; 1090

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&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1090

Asp Thr Met Lys Gln Lys Ser

1

5

&lt;210&gt; 1091

&lt;211&gt; 7

&lt;212&gt; PRT

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&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1091

Asp Thr Met Lys Gln Arg Ser

1

5

&lt;210&gt; 1092

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1092

Asp Thr Met Lys Gln His Ser

1

5

&lt;210&gt; 1093

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1093

Asp Thr Met Lys Gln Pro Ser

1

5

&lt;210&gt; 1094

&lt;211&gt; 7

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<210> 1202

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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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substitutions

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&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1207

Asp Thr Met Leu Gln His Ser

1

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&lt;210&gt; 1208

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1208

Asp Thr Met Leu Gln Pro Ser

1

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&lt;210&gt; 1209

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1209

Asp Thr Met Leu Gln Thr Ser

1

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&lt;210&gt; 1210

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1210

Asp Thr Met Leu Gln Asp Ser

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&lt;210&gt; 1211

&lt;211&gt; 7

&lt;212&gt; PRT

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&lt;210&gt; 1216

&lt;211&gt; 7

&lt;212&gt; PRT

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antibody and further modified by amino acid  
substitutions

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&lt;210&gt; 1217

&lt;211&gt; 7

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antibody and further modified by amino acid  
substitutions

&lt;400&gt; 1217

Asp Thr Lys Lys Leu Thr Ser  
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&lt;210&gt; 1218

&lt;211&gt; 7

&lt;212&gt; PRT

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 1218

Asp Thr Lys Lys Leu Asp Ser  
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&lt;210&gt; 1219

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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antibody and further modified by amino acid  
substitutions

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&lt;210&gt; 1220

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1220

Asp Thr Lys Lys His Ser Ser

1

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&lt;210&gt; 1221

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1221

Asp Thr Lys Lys His Lys Ser

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&lt;210&gt; 1222

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1222

Asp Thr Lys Lys His Arg Ser

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&lt;210&gt; 1223

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1223

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&lt;210&gt; 1224

&lt;211&gt; 7

&lt;212&gt; PRT



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<210> 1229

<211> 7

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<210> 1230

<211> 7

<212> PRT

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<210> 1231

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<210> 1232

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<212> PRT

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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

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<210> 1236

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antibody and further modified by amino acid  
substitutions

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<210> 1239  
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<210> 1240  
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antibody and further modified by amino acid  
substitutions

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<210> 1242

<211> 7

<212> PRT

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antibody and further modified by amino acid  
substitutions

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<210> 1243

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antibody and further modified by amino acid  
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<210> 1244

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antibody and further modified by amino acid  
substitutions

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<210> 1245

<211> 7

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antibody and further modified by amino acid  
substitutions

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<210> 1246

<211> 7

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antibody and further modified by amino acid  
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<210> 1247

<211> 7

<212> PRT

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antibody and further modified by amino acid  
substitutions

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<210> 1248

<211> 7

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antibody and further modified by amino acid  
substitutions

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Asp Thr Lys Gly His Pro Ser  
1 5

<210> 1249

<211> 7

<212> PRT

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<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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<210> 1250

<211> 7

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<210> 1251  
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<220>  
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<210> 1252  
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<210> 1253  
<211> 7  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

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Asp Thr Lys Gly Gln Lys Ser  
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<210> 1254  
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antibody and further modified by amino acid  
substitutions

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<210> 1255

<211> 7

<212> PRT

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 1255

Asp Thr Lys Gly Gln His Ser  
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<210> 1256

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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<210> 1257

<211> 7

<212> PRT

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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<210> 1258

<211> 7

<212> PRT

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 1258

Asp Thr Lys Gly Gln Asp Ser



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&lt;210&gt; 1259

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1259

Asp Thr Lys Arg Leu Ala Ser

1

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&lt;210&gt; 1260

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1260

Asp Thr Lys Arg Leu Ser Ser

1

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&lt;210&gt; 1261

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1261

Asp Thr Lys Arg Leu Lys Ser

1

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&lt;210&gt; 1262

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1262

Asp Thr Lys Arg Leu Arg Ser

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&lt;210&gt; 1263

&lt;211&gt; 7

<212> PRT  
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<220>  
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Asp Thr Lys Arg Leu His Ser  
1 5

<210> 1264  
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<220>  
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<210> 1265  
<211> 7  
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Asp Thr Lys Arg Leu Thr Ser  
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<210> 1266  
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Asp Thr Lys Arg Leu Asp Ser  
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<210> 1267  
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<212> PRT  
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antibody and further modified by amino acid  
substitutions

<400> 1267

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1 5

<210> 1268

<211> 7

<212> PRT

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<220>

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 1268

Asp Thr Lys Arg His Ser Ser  
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<210> 1269

<211> 7

<212> PRT

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antibody and further modified by amino acid  
substitutions

<400> 1269

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1 5

<210> 1270

<211> 7

<212> PRT

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 1270

Asp Thr Lys Arg His Arg Ser  
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<210> 1271

<211> 7

<212> PRT

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antibody and further modified by amino acid  
substitutions

<400> 1271

Asp Thr Lys Arg His His Ser

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&lt;210&gt; 1272

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1272

Asp Thr Lys Arg His Pro Ser

1

5

&lt;210&gt; 1273

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1273

Asp Thr Lys Arg His Thr Ser

1

5

&lt;210&gt; 1274

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1274

Asp Thr Lys Arg His Asp Ser

1

5

&lt;210&gt; 1275

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1275

Asp Thr Lys Arg Gln Ala Ser

1

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&lt;210&gt; 1276

&lt;211&gt; 7

&lt;212&gt; PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 1276

Asp Thr Lys Arg Gln Ser Ser  
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<210> 1277

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 1277

Asp Thr Lys Arg Gln Lys Ser  
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<210> 1278

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 1278

Asp Thr Lys Arg Gln Arg Ser  
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<210> 1279

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<212> PRT

<213> Artificial Sequence

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<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 1279

Asp Thr Lys Arg Gln His Ser  
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<210> 1280

<211> 7

<212> PRT

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&lt;400&gt; 1280

Asp Thr Lys Arg Gln Pro Ser  
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&lt;210&gt; 1281

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 1281

Asp Thr Lys Arg Gln Thr Ser  
1 5

&lt;210&gt; 1282

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 1282

Asp Thr Lys Arg Gln Asp Ser  
1 5

&lt;210&gt; 1283

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 1283

Asp Thr Lys Tyr Leu Ala Ser  
1 5

&lt;210&gt; 1284

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

&lt;400&gt; 1284

Asp Thr Lys Tyr Leu Ser Ser

1 5

<210> 1285  
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Asp Thr Lys Tyr Leu Lys Ser  
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<210> 1286  
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<400> 1286  
Asp Thr Lys Tyr Leu Arg Ser  
1 5

<210> 1287  
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<220>  
<223> Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

<400> 1287  
Asp Thr Lys Tyr Leu His Ser  
1 5

<210> 1288  
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<400> 1288  
Asp Thr Lys Tyr Leu Pro Ser  
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<210> 1289  
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antibody and further modified by amino acid  
substitutions

<400> 1289  
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<210> 1290  
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<212> PRT  
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substitutions

<400> 1290  
Asp Thr Lys Tyr Leu Asp Ser  
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<210> 1291  
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antibody and further modified by amino acid  
substitutions

<400> 1291  
Asp Thr Lys Tyr His Ala Ser  
1 5

<210> 1292  
<211> 7  
<212> PRT  
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<211> 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<210> 1302

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<210> 1307

<211> 7

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<210> 1308

<211> 7

<212> PRT

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<211> 7

<212> PRT

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<211> 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<212> PRT

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antibody and further modified by amino acid  
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<210> 1322

<211> 7

<212> PRT

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antibody and further modified by amino acid  
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1 5

<210> 1323

<211> 7

<212> PRT

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antibody and further modified by amino acid  
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1 5

<210> 1324

<211> 7

<212> PRT

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<210> 1327

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<210> 1328

<211> 7



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<220>  
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antibody and further modified by amino acid  
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1 5

<210> 1329  
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antibody and further modified by amino acid  
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<210> 1330  
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antibody and further modified by amino acid  
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<210> 1331  
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antibody and further modified by amino acid  
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<210> 1332  
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antibody and further modified by amino acid  
substitutions

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<210> 1333

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antibody and further modified by amino acid  
substitutions

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<210> 1334

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antibody and further modified by amino acid  
substitutions

<400> 1334

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<210> 1335

<211> 7

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

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<210> 1336

<211> 7

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<223> Amino acid sequence derived from Murine monoclonal  
antibody and further modified by amino acid  
substitutions

<400> 1336

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&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;400&gt; 1337

Asp Thr Lys Leu Leu Thr Ser

1

5

&lt;210&gt; 1338

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1338

Asp Thr Lys Leu Leu Asp Ser

1

5

&lt;210&gt; 1339

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1339

Asp Thr Lys Leu His Ala Ser

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&lt;210&gt; 1340

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1340

Asp Thr Lys Leu His Ser Ser

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&lt;210&gt; 1341

&lt;211&gt; 7

&lt;212&gt; PRT

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<400> 1341

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<210> 1342

<211> 7

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<210> 1343

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<220>

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<210> 1344

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<210> 1345

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substitutions

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<210> 1346

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antibody and further modified by amino acid  
substitutions

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<210> 1347

<211> 7

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antibody and further modified by amino acid  
substitutions

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<210> 1348

<211> 7

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antibody and further modified by amino acid  
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<210> 1349

<211> 7

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antibody and further modified by amino acid  
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&lt;210&gt; 1350

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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1350

Asp Thr Lys Leu Gln Arg Ser

1

5

&lt;210&gt; 1351

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1351

Asp Thr Lys Leu Gln His Ser

1

5

&lt;210&gt; 1352

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1352

Asp Thr Lys Leu Gln Pro Ser

1

5

&lt;210&gt; 1353

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Amino acid sequence derived from Murine monoclonal antibody and further modified by amino acid substitutions

&lt;400&gt; 1353

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&lt;210&gt; 1354

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<210> 1355

<211> 7

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<210> 1356

<211> 7

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<400> 1356

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<210> 1357

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<400> 1357

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<210> 1358

<211> 7

<212> PRT

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<400> 1358

Asp Thr Leu Lys Leu His Ser  
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<210> 1359

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<210> 1360

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<400> 1361

Asp Thr Leu Lys His Ala Ser  
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<210> 1362

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<400> 1362

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antibody and further modified by amino acid  
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<210> 1364

<211> 7

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
substitutions

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antibody and further modified by amino acid  
substitutions

<400> 1366

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antibody and further modified by amino acid  
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<400> 1367  
Asp Thr Leu Lys His Thr Ser  
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<210> 1368  
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antibody and further modified by amino acid  
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<400> 1368  
Asp Thr Leu Lys His Asp Ser  
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<210> 1369  
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antibody and further modified by amino acid  
substitutions

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<210> 1370  
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antibody and further modified by amino acid  
substitutions

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Asp Thr Leu Lys Gln Lys Ser  
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<210> 1372

<211> 7

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<213> Artificial Sequence

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<210> 1373

<211> 7

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<213> Artificial Sequence

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Asp Thr Leu Lys Gln His Ser  
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<210> 1374

<211> 7

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<400> 1374

Asp Thr Leu Lys Gln Pro Ser  
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antibody and further modified by amino acid  
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<210> 1377

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<210> 1379

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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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antibody and further modified by amino acid  
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<210> 1463

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<210> 1475

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<210> 1483

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substitutions

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antibody and further modified by amino acid  
substitutions

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<210> 1486  
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